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Therapeutically Equivalent Drugs; Availability of List

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 20

[Docket No. 78N-0170]

Therapeutically Equivalent Drugs; Availability of List

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its public information regulations to make available a list of FDA-approved prescription drug products, together with therapeutic equivalence evaluations of products in the List that are available from more than one source. This document announces the availability of the Approved Prescription Drug Products List (the List), and responds to the public comments received on the proposed policy of making such a list available and on the content and format of the List.

EFFECTIVE DATE: December 1, 1980.

FOR FURTHER INFORMATION CONTACT: Howard P. Muller, Jr., Bureau of Drugs (HFD-30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5220.

ADDRESS: Copies of the Approved Prescription Drug Products List may be obtained from: United States Government Printing Office, Washington, DC 20402 (refer to the publication by name).

SUPPLEMENTAL INFORMATION: In the **Federal Register** of January 12, 1979 (44 FR 2932), FDA proposed to amend § 20.117 (21 CFR 20.117) of its public information regulations to include in the list of available computer printouts approved prescription drug products with therapeutic equivalence evaluations. "Approved prescription drug products" refers to prescription drug products approved by FDA through new drug applications (NDA's) or abbreviated new drug applications (ANDA's) under the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) or, in the case of antibiotics, through analogous applications known as Form 5's or Form 6's under section 507 of the act (21 U.S.C. 357). All drug products on the List have been fully reviewed and approved for safety and effectiveness by FDA. The List also includes therapeutic equivalence evaluations for multiple-source drug products. Those products on the List that are evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent therapeutic effect and equivalent potential for adverse effects when administered to the patient under the conditions specified in the labeling.

The List, which was prepared in response to requests from State health agencies for assistance in administering their drug product selection laws, was presented as a proposal so that interested persons could review and comment on the List and all aspects of the **Federal Register** proposal. The agency received more than 100 comments addressing most points covered in the proposal and the preface to the List, and also concerning specific drug products included or not included in the List. This document responds only to comments concerning the proposed policy of making this List available and to the comments on the preface (Part I) of the List. FDA is responding individually to comments about specific product listings (Part II of the List).

Although a number of comments opposed the preparation of the List, many comments supported the List by agreeing with statements made in the proposal and in the preface to the List. Many of these comments were from elderly persons on fixed incomes who said that they used drug products frequently. They urged FDA to help their physicians and pharmacists provide them with drug products that are less expensive and yet therapeutically equivalent. Other comments in support of the List came from Federal, State, and local health-related agencies and private institutions and organizations urging that FDA take action to foster the availability of less expensive, therapeutically equivalent drug products.

The regulation is being finalized essentially as proposed, 44 FR 2932, January 12, 1979. A few changes have been made, however, for clarification. The word "all" in the first line of the regulation has been deleted, and the word "marketed" has been added to the regulation. This reflects FDA's policy to include on the List only those prescription drug products that have been approved for marketing under sections 505 and 507 of the act, and which are currently being marketed. FDA will remove from the List any drug product which is no longer being marketed, even though there remains an approved application for that product. Unmarketed products may periodically appear on the List, however, until FDA becomes aware of their nonmarketed status. Conversely, when FDA becomes aware through the application review process that an approved drug product is being remarketed, it will again be included on the List. The proposed regulation has also been amended by deleting all references to "certificate holder" or "certificate." As explained in the preface to the List under Part E, "Precautions to Users of the List," the List identifies only the holder of the approved application in FDA files. Finally, the phrase "route of administration" was inadvertently left out of the proposal and has been added to the final regulation.

A summary of the substantive comments and the agency's responses follow:

I. Policy Considerations in Proposing List

1. One comment cited a journal article which included a survey finding that only 21 perent of those over 65 years of age were willing to accept a less expensive generic equivalent prescription. The survey also found that of those age 56 to 64, only 30 percent would accept a substitute drug. The comment concluded, based on this survey, that prescription drug users who are over age 56 are responsible for the lack of product substitution, rather than health professionals and the drug industry, as FDA contended in the proposal.

The agency believes that the article cited by the comment does not contain sufficient information about the survey for FDA to comment on its results. Even so, FDA notes that the article concluded: "It appears that a program of educating the elderly to the safety, efficacy, and economic merits of accepting equivalent products when not restricted by their physicians is in order." The agency agrees that reluctance in choosing less expensive duplicate prescription drug products in the place of more expensive brand name prescription drugs may be caused largely by a lack of information about the safety, effectiveness, and therapeutic equivalence of the duplicate drug products. FDA believes that the information provided by the List will help to lessen doubts that may exist regarding the safety, effectiveness, and economic advantage of therapeutically equivalent duplicate drug products.

2. Another comment said that the public would not be educated by the publication of the List as contended by FDA in the proposal. The comment said that while most people would know that a List exists, only a few would be familiar with the List's contents.

The agency believes that publication of the List will lend to increased consumer awareness of less expensive therapeutically equivalent prescription drug products. The availability of the List is announced in this **Federal**

Register document and copies will be provided to State health agencies. The release of such information usually prompts coverage in the public and trade press, which in turn broadens consumer awareness. Such increased awareness should stimulate greater consumer demand for less expensive therapeutic equivalents, and physicians and pharmacists should be influenced to respond to that demand by prescribing and dispensing such less expensive drug products.

3. One comment questioned FDA's statements in the proposal that the absence of a list of therapeutically equivalent drug products permits the continuation of a situation involving potential dangers to health as well as deception to consumers, because FDA has repeatedly assured the public that drug products on the market are safe and effective, that defective products will be quickly removed, and that advertising and promotion are monitored. The comment asked how FDA recognized dangers in the absence of a list and how the List would negate such dangers.

The agency believes that the publication of the information contained in the List will protect the public health by helping to eliminate a situation involving potential dangers to health as well as deception of consumers. First, in the absence of an official List, pharmacists or other persons responsible for pharmacy or institutional drug purchasing would be required to make their own evaluations of therapeutic equivalence. Such an evaluation, without the information that will be provided by the List, presents a risk that drug products that are not therapeutically equivalent may be purchased for substitution, with possible adverse health consequences to patients. Second, a List of therapeutically equivalent drug products is needed to balance and correct allegations about the therapeutic inequivalence of drug products that have appeared, for example, in advertisements in newspapers and on radio and television. These allegations imply that the minimum standards for drug quality are inadequate to assure such quality, that differences in pharmaceutically equivalent drug products generally produce differences in therapeutic effects, and that government regulation never assures therapeutic equivalence. FDA believes that the broad dissemination of these allegations to the general public, as well as to health professionals, may lead to a decline of public confidence in the quality of the nation's drug supply. For this reason, an authoritative statement from the Federal agency charged with monitoring and assuring the safety, effectiveness, and quality of drugs is needed.

It is also important to note that, contrary to what is implied in the comment, the absence of a list of therapeutically equivalent drug products does not mean that drug products on the market are not safe and effective, or that defective products will not be quickly removed, or that the agency is not monitoring advertising and promotion. The List is simply a compilation of those marketed drug products that have been approved by FDA under sections 505 and 507 of the act, with certain exceptions as explained in the proposal (at pp. 2948–2949) and elsewhere in this document. These products have already been fully reviewed and approved for safety and effectiveness by FDA. The List also includes therapeutic equivalence evaluations for those approved prescription drug products that are available from more than one source. Drug products evaluated as therapeutically equivalent are pharmaceutical equivalents that can be expected to give the same therapeutic effect when administered to the patient under the conditions specified in the labeling.

4. A comment contended that although the List may have been desirable a decade ago, it now is counterproductive. The comment argued that manufacturers of generic products have ample resources to promote their products without FDA "assistance", and that they foster their own image, their reputation for quality, and the benefits of substitution by a variety of means. Furthermore, the comment argued, health professionals today may easily obtain reliable information on generic drug products from manufacturers, distributors, medical journals, pharmacy journals, academic institutions, and individual expertise. The comment asserted that the fact that more than 40 States now permit generic substitution proves that these resources have already been effectively used.

The agency believes that publication of the List now would not be counterproductive merely because progress has already been made in generic drug product selection. All persons involved in drug product selection need accurate, complete, and understandable information about therapeutically equivalent prescription drug products. Such information properly may come from the Federal agency charged with monitoring and assuring the safety, effectiveness, and quality of the nation's drug supply. Pharmacies, hospitals, States, and private and public institutions and organizations continue to ask FDA to share its broad knowledge of the safety and effectiveness of drug products, so that they can continue to carry out their duties to protect and promote the public health, provide health care services safely and with efficiency and cost-effectiveness, and advise physicians and pharmacists on drug product selection.

5. One comment said that the Model State Drug Product Selection Act (Model Act) is intended to encourage and implement generic drug product substitution, and that the FDA List is purportedly not intended to be used for drug substitution—it is not, as stated in the proposal, a recommendation of which products persons should purchase, prescribe, or dispense. However, the comment said, the Model Act would require that each State formulary include all drug products determined by FDA to be therapeutically equivalent. The comment concluded that when combined with the Model Act, the FDA List is intended to be used for drug substitution.

Although FDA acknowledges that the List is intended, among other things, to assist the States in implementing drug product selection laws, the List is not a recommendation of which products to purchase, prescribe, or dispense. The Model Act, a joint effort of the Department of Health and Human Services (DHHS) and the Federal Trade Commission (FTC), is being made available to the States to assist them in enacting their own drug product selection legislation. The Model Act, if chosen by a State as a guide, would require an appropriate State health agency to establish a formulary that would list equivalent drug products, potentially including all drug products determined by FDA to be therapeutically equivalent. As one aspect of DHHS's cooperation with FTC, FDA has been asked to prepare a List of such products to be provided to the States. Thus, the List is intended to assist the States in establishing a formulary that would list therapeutically equivalent drug products; it is not intended to designate any drug products as preferable to others for purposes of generic substitution.

6. One comment contended that FDA has attempted to suppress the industry's right to be heard, to prevent open, uncensored discussion of the issues, and to destroy the credibility of the pharmaceutical industry in refusing to publish in the proposal the objections to

the List set forth in PMA's lawsuit to challenge the List. *Pharmaceutical Manufacturers Ass'n* v. *Kennedy*, 471 F. Supp. 1224 (D.Md. 1979). The comment said that this decision is especially offensive in view of the comprehensive nature of the Federal Register proposal.

The agency disagrees with this comment and believes that the issue it raises was adequately addressed in the proposal, which states at p. 2936:

> The objections of PMA to an FDA list of therapeutically equivalent drug products, as set forth in its complaint, need not be discussed point-by-point in this document. This preamble amply describes the reasons for issuing such a list, the legal, scientific, and regulatory bases on which such a list may be prepared and issued and the details of the list that FDA proposes to issue. Opportunity to comment and raise specific objections, in light of the specific proposal in this notice, is being provided to the public, including PMA. The objections of PMA, both in its complaint and, if PMA chooses, as particularized by its comments on this proposal, will be considered by FDA in determining how to proceed in this matter.

II. Legal Authority and Legal Status

7. One comment contended that it is beyond FDA's regulatory authority to make a judgment of therapeutic equivalence. The comment said that it is within FDA's authority to establish regulatory requirements for drug products intended for marketing, and to require those wishing to market such products to provide sufficient documentation assuring that the products meet those regulatory requirements. The only comparison of drug products that FDA could make based on this information, the comment asserted, would be an evaluation of the degree to which such products meet the established regulatory requirements, which do not include standards for therapeutic equivalence. Another comment said the List should be enacted through the Congressional legislative process and not by a regulatory agency.

FDA has concluded that it does have the authority to determine therapeutic equivalence on the basis of criteria explained in the proposal. FDA evaluates as therapeutically equivalent approved drug products that meet the following general criteria: (1) They are pharmaceutical equivalents in that (a) they contain identical amounts of the same acitve drug ingredient in the same dosage form; and (b) they meet compendial or other applicable standards of identity, strength, quality, and purity; (2) they are bioequivalent in that (a) they do not present a known or potential bioinequivalence problem; or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (3) they are adequately labeled; and (4) they are manufactured in compliance with current good manufacturing practice. These four criteria are applied to information already contained in FDA files regarding the safety, effectiveness, and quality of approved prescription drug products to make a nonregulatory evaluation of therapeutic equivalence. The four criteria are regulatory determinations which FDA is statutorily authorized to make. FDA's authority to require that drug products meet compendial standards is based on section 501(b) of the act; to require that certain drug products meet bioequivalency requirements on sections 201(p), 502, 505, and 701(a) of the act; to require adequate labeling on sections 502, 505, and 507 of the act, and 21 CFR 201.100; and to require compliance with current good manufacturing practice regulations on sections 501(a)(2)(B) and 701(a) of the act. The Degree to which drug products are found to be therapeutically equivalent is determined by the degree to which they meet the four criteria. This is a nonregulatory evaluation in which the agency simply applies the four criteria to drug product information in FDA files. Furthermore, the therapeutic equivalence evaluations do not constitute an order or a rule, they do not impose a requirement or restriction, nor do they constitute determinations that any products are in violation of the act or that any products are preferable to others.

FDA is authorized to make public its therapeutic equivalence evaluations on the basis of the following statutory provisions: section 310 of the Public Health Service Act directs the Secretary (whose authority is delegated to the Commissioner of Food and Drugs (21 CFR 5.1(a)(2))) to issue "information related to public health, in the form of publications or otherwise, for the use of the public" and to publish "other pertinent health information for the use of persons and institutions concerned with health services." Section 311(a) of the Public Health Serivce Act directs the Secretary to "advise the several States on matters relating to the preservation and improvement of the public health". Section 705(b) of the Federal Food, Drug, and Cosmetic Act authorizes the Secretary to disseminate information about drugs "in situations involving, in the opinion of the Secretary, imminent danger to health, or gross deception of the consumer." Section 306 of the act authorizes FDA to use written notices in place of formal enforcement actions when the public interest will be adequately served by such notices.

Regarding the comment that the List should be enacted through the Congressional legislative process and not by FDA, the agency believes that Congress authorized FDA's publication of the List through the statutory provisions cited in the preceding paragraph.

8. Several comments argued that FDA's reliance on section 705(b) of the act (21 U.S.C. 375(b)) is incorrect. Section 705(b) states in part: "The Secretary may also cause to be disseminated information regarding foods, drugs, devices or cosmetics in situations involving, in the opinion of the Secretary, imminent danger to health or gross deception to the consumer." The comments said that FDA's reliance upon this section is misapplied because the agency has not indicated an "imminent danger to health or gross deception of the consumer." FDA has only cited newspaper advertisements and radio and television spot announcements directed to the public which the agency believes are misleading. Such examples, the comments said, can hardly be classified as an "imminent danger." Furthermore, the comments said that the limitations imposed by section 705(b) of the act reflect congressional consideration of the agency's use of publicity. The comments explained that the legislative history of section 705(b) of the act shows that FDA was deliberately denied the discretion it now claims and that the agency was forbidden to interfere with competition among legally marketed prescription drug products solely to promote policy. The comments said that Congress considered and rejected an earlier version of secton 705(b) of the act that would have broadly authorized the Secretary to disseminate "such information regarding any food, drug, or cosmetic as he deems necessary in the interest of public health." By adopting the limited terms of section 705(b) of the act, the comment said, Congress deliberately circumscribed the agency's authority to use its influence to persuade the public to purchase or refrain from purchasing legally marketed products.

The agency disagrees with the comment that reliance on the section 705(b) of the act is misapplied. In relying on that section, the magnitude of the potential danger or deception need not be estimated because that section is not a limitation upon the authority of the agency. Rather, as explained in the proposal (at p. 2936), this statutory provision places within the express scope of the Secretary's duties

something that is one of the Secretary's implied functions. *Hoxsey Cancer Clinic* v. *Folson*, 155 F. Supp. 376, 378 (D.D.C. 1957). Because section 705(b) of the act merely expresses an implicit power of the Secretary and the Commissioner, it is not necessary to determine whether the specific conditions for invoking the explicit authority under that section now exists. It is important to note, however, that potential dangers do exist. Currently, in the absence of an official List, pharmacists would be required to make their own evaluations of therapeutic equivalence, usually without the comprehensive information available to the agency. Such evaluations without adequate information create a risk that drug products that are not therapeutically equivalent may be substituted and dispensed, with possible adverse health consequences to patients. In addition, a list of therapeutically equivalent drug products is needed to balance and correct deceptive materials disseminated widely in recent years alleging the therapeutic inequivalence of drug products. Many publications and other media still imply that the minimum standards for drug quality are inadequate to ensure such quality, that differences in pharmaceutically equivalent drug products generally produce differences in therapeutic effects, and that government regulation never assures therapeutic equivalence. The broad dissemination of these assertions to the general public, as well as to health professionals, may lead to a decline of public confidence in the quality of the nation's drug supply.

Regarding the comment that by adopting the more limited terms of section 705(b) of the act, Congress circumscribed FDA's authority to use its influence to persuade the public to purchase or refrain from purchasing legally marketed products, FDA does not believe that the List is an effort to persuade the public. The List contains only public information and advice; it imposes no requirement or restriction upon any person; it makes no recommendations as to which products persons should purchase, prescribe, or dispense, or, conversely, which products should be avoided. The List actually enhances the public's freedom of choice by providing information necessary to a decision whether a brand name drug or its therapeutically equivalent substitute should be selected.

9. Another comment said that the Federal Food, Drug, and Cosmetic Act precludes FDA from judging the therapeutic equivalence of different drugs as part of the new drug approval process. In evaluating new drug applications, the comment said FDA's role is limited to a review of the safety and efficacy of drugs. The comment explained that the legislative history of the 1962 amendments to the act shows that judging relative efficacy among different drugs is not a proper function for FDA. The comment said that therapeutic equivalence as used in the proposal is akin to relative efficacy as considered in 1962 because the preamble, in discussing the concepts of therapeutic equivalence and bioequivalence, discusses them in terms of the efficacy of drug products.

It is the agency's position that the part played by the new drug approval process in FDA's determination of therapeutic equivalence does not expand that process beyond a review of the safety and effectiveness of drug products. As explained in the response to the first comment in this Part, FDA evaluates as therapeutically equivalent those drug products that meet four general criteria. In addition, there are three major elements which comprise the scientific and regulatory foundations underlying the four general criteria: (1) Pharmaceutical equivalence, (2) bioequivalence, and (3) controls to ensure consistency of quality in, and pharmaceutical equivalence and bioequivalence among, individual batches produced by all manufacturers. This third element includes FDA's new drug approval process, as well as the antibiotic certification processes, the batch certification procedures, the good manufacturing practice regulations, and FDA's monitoring of the marketplace. The new drug approval process is an important part of FDA's program for determining the therapeutic equivalence of drug products. The process of reviewing and approving new drug applications enables FDA, in addition to determining pharmaceutical equivalence and bioequivalence of the drug products, to review the inactive ingredients in the drug products, to ensure the adequacy of labeling, and to evaluate any proposed specific manufacturing controls to ensure appropriate quality and batch-to-batch consistency. Only when all these elements meet regulatory requirements may an application be approved. Although the information submitted in support of a new drug application is part of the information FDA uses to make a therapeutic equivalence determination, a determination of therapeutic equivalence is separate from the new drug approval process. FDA emphasizes that it will continue to approve new drug applications only on the basis of safety, effectiveness, and any bioavailability requirement.

In addition, FDA's determination of therapeutic equivalence does not involve a judgment of relative efficacy. Relative efficacy refers to a comparison of the effectiveness of different therapeutic moieties, whereas therapeutic equivalence determinations involve different manufacturers' products containing the same active drug ingredients. Moreover, FDA's determination of therapeutic equivalence is not a judgment as to which manufacturer's product is "better" or "more effective."

10. Several comments charged that the agency is circumventing the express restrictions of section 705(b) of the act by invoking the generalized grants of publication authority conferred by the Public Health Service Act. The comments contended that in interpreting statutes the general must give way to the specific. The Public Health Service Act must be construed in harmony with section 705(b) to mean that only in limited circumstances should FDA enter the competitive arena on behalf of or against specific products. The comments also said that the dissemination of information envisioned by the Public Health Service Act relates to neutral scientific and epidemiological data designed to improve the quality of health care services. The comments explained that the publication grant codified in section 310 of the Public Health Service Act derives from former 42 U.S.C. 7, which authorized the study, investigation, and release of information related to the "diseases of man and conditions influencing the propagation and spread thereof." The original legislation was directed toward health rather than economic concerns, argued the comments, and there is no basis for supposing that the Public Health Service Act was intended to give the FDA authority to officially rate specific drug products in a purported effort to decrease consumer costs. The comments also said that the grant of authority in section 311(a) of the Public Health Service Act for advice to the States on public health matters cannot properly be read as giving FDA the power to prepare and disseminate the proposed List. To do so, said the comments, would not only displace the traditional authority of health professionals to independently judge the comparative quality of prescription drug products, but would redistribute the primary control of prescribing and dispensing from the States to the Federal Government.

The agency disagrees with the contention that FDA has incorrectly

interpreted and applied the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. As explained in the response to comment 8 above, the agency does not agree that section 705(b) limits FDA's authority in this area, nor does it restrict FDA's application of the Public Health Service Act. In addition, publication of the List conforms exactly to the direction of sections 310 and 311(a) of the Public Health Service Act. The availability of approved drug products evaluated by FDA as therapeutically equivalent, as well as the identity of pharmaceutically equivalent drug products which are evaluated by FDA as not therapeutically equivalent, is important information related to the public health. The List provide information that is useful to persons and institutions concerned with health services, and it compiles information in FDA files that is relevant to drug product selection for use by those consumers, institutions, and State agencies who want it.

The agency also disagrees with the comment that the List usurps the authority of health professionals. An FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing drug products with due care to individual patients. If the characteristics of a specific product are important in the therapy of a particular patient, the physician's specification of that product is appropriate. FDA recognizes that drug products that are therapeutically equivalent may still vary, for example, in color, shape, taste, or packaging and patients may not perceive them as identical or equally acceptable. For this reason, these drug products are not substitutable or interchangeable in all cases. FDA does not determine whether different drug products are substitutable or interchangeable for use by a particular patient; rather, this judgment rests with the practictioner who, in prescribing and dispensing drug products, can consider the unique characteristics, needs, or problems of the patient. Pharmacists, in dispensing drug products, must be familiar with, for example, the expiration times and labeling conditions for storage, particularly for reconstituted products, to ensure that patients are properly advised when one product is substituted for another.

Finally, the agency disagrees that the List would infringe on the States' authority in regulating the prescribing and dispensing of drug products. The List is intended to assist the States in carrying out their duties to protect and promote the public health, both in providing health care services safely and with efficiency and cost-effectiveness, and in advising physicians and pharmacists of the requirements of State drug product selection laws. The States continue to ask FDA to share its broad knowledge of the safety, effectiveness, and quality of the nation's drug supply.

11. Several comments said that the notice-and-comment procedure followed in adopting the List unlawfuly denies manufacturers and the general public the right to an evidentiary hearing. Some comments contended that an evidentiary hearing is necessary because the List will have a substantial economic and legal impact on drug manufacturers, and that physicians, pharmacists, consumers, and State agencies will be relying heavily on the List to select drug products and to develop State formularies. The comments contended that only the evidentiary hearing procedure would guarantee the accuracy and reliability of the final version of the List. The comments said that each determination of therapeutic equivalance in the List, if questioned by the manufacturer, deserves an adjudicatory hearing. Further, the comments said it is impossible for manufacturers, especially those with several drugs evaluated on the List, to adequately review all relevant available data bearing on the equivalence issues within the notice-and-comment period permitted.

Other comments contended that a hearing is required because of various types of factual determinations that are involved in the therapeutic equivalence determination. One drug manufacturer requested an evidentiary hearing concerning FDA's specific findings on the bioavailability or bioequivalence of its drug products. The comment said its products would be adversely affected because FDA intends that the List be used to influence the substitution of a second drug product for the drug product first prescribed. Another comment said that the therapeutic equivalence information proposed for the List may include official fact findings and declarations relating to specific drug products and manufacturers. Essential to each of these determinations, the comment contended, is a complex appraisal of scientific facts as well as an individual evaluation of manufacturer processes and quality control procedures. The comment said that these particular fact-oriented inquiries must be made in an adjudicatory setting. Another comment explained that the Federal Food, Drug, and Cosmetic Act provides procedures for determining the effectiveness of new drugs. Those procedures, the comment said, provide that a party aggrieved by FDA decisions concerning the effectiveness of that product has the opportunity to an evidentiary hearing to challenge the correctness and evidentiary basis of that decision. The comment contended that FDA's determinations of therapeutic equivalence are decisions concerning the effectiveness of the drug products considered equivalent, and the aggrieved manufacturer is entitled to an evidentiary hearing concerning the correctness and evidentiary basis for such decisions. The comment said that any other interpretation of the act would enable FDA to make public assertions about the effectiveness of a manufacturer's approved product that would have the practical effect of amending the labeling for that product without giving the manufacturer the opportunity to be heard and to challenge in an evidentiary proceeding the basis for such assertions. One comment said that when FDA publicly declares that drug products in a group containing the same active ingredient are therapeutically equivalent, the agency claims comparative efficacy or quality for each approved product in the group. The comment claimed that equivalence judgments such as these are, in effect, new claims for the products. If a manufacturer made a similar equivalence claim, the comment said, that manufacturer would be required to submit a supplemental application to amend its NDA (or ANDA) to encompass the additional claim (21 CFR 314.8(a)(4)(ii)). Such an application would trigger the adjudicatory procedures provided by statute for regulatory approvals, which include the right to request an evidentiary hearing. Similarly, another comment said in making therapeutic equivalence determinations, FDA should give notice that it is proposing to amend all approved NDA's (or ANDA's) for products containing the active ingredient to include the claim of therapeutic equivalence (21 CFR 314.200(a)). The comment said that each notice should cite all data and arguments that the agency relied on to substantiate the new claim, and should advise affected parties of their opportunity for a hearing (21 CFR 314.200(b)). The comment also said that if a hearing is subsequently requested, it should be granted in any case in which the requestor demonstrates that there is a genuine and substantial issue of

material fact as to the accuracy of the proposed claim. (21 CFR 314.200(g)(6).)

FDA is of the opinion that publication of the List does not require an evidentiary hearing. The agency believes that most of the comments misconstrue the legal status of the List. As explained in the proposal (at p. 2937), the List contains only public information and advice. It does not constitute an order or a rule as defined in the Administrative Procedure Act (5 U.S.C. 551(4)) and, consequently, adherence to the rulemaking procedures of that statute (5 U.S.C. 553) is not required. The List neither determines nor adjudicates the legal rights of any drug manufacturer or distributor; it does not impose any requirement or restriction upon any person; it does not interpret or apply the act in a manner that creates any obligation on any person; it makes no recommendation as to which products persons should purchase, prescribe, or dispense, or conversely, which products should be avoided. To the extent that the List identifies drug products approved for marketing under sections 505 and 507 of the act, it merely sets forth information to which the public is entitled under the Freedom of Information Act. Exclusion of a drug product from the List would not necessarily mean that the drug product is in violation of section 505 or 507 of the act, or that it is not safe or effective, or that it may not be therapeutically equivalent to other drug products. (For reasons explained on pages 2948–2952 of the proposal, several classes of drug products are excluded from the List: for example, prescription drug products approved as safe for marketing prior to 1962 and not yet determined to be effective, and drug products that have not been reviewed and approved through the new drug or antibiotic approval process.) Decisions on whether specific drug products are subject to the requirements of either section 505 or 507, or whether specific drug products have fulfilled those requirements, are made in clearly defined proceedings unrelated to the release of information on approval decisions. To the extent that the List sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public and to the States regarding an important public health matter. These evaluations do not constitute determinations that any products are in violation of the act or that any products are preferable to others. These are nonregulatory evaluations that are based on the application of certain criteria to information contained in FDA files.

Most of the reasons cited by the comments for demanding an evidentiary hearing (for example, determinations of effectiveness and bioequivalence) concern determinations that were made by FDA in clearly defined proceedings when there existed the right to an evidentiary hearing. Thus, the notice and comment procedure used in adopting this List is sufficient.

The purely advisory character of the List was recognized by the court in P.M.A.'s unsuccessful attempt to enjoin FDA from issuing the List, *P.M.A.* v. *Kennedy, supra* at 1229, 1231, in which the court observed:

> The information contained in the Drug List includes a list of approved drug products found by FDA to be safe and effective as well as therapeutically equivalent to each other * * *. There is nothing to indicate that the Drug List and Price Guide do any more than list or compile data which has already been obtained via statutory procedure * * *. No agency is ordering any PMA member to engage in or refrain from any action. Nor is any agency doing anything which is binding on the parties.

FDA also believes that § 314.200(a), (b), and (g)(6), which provide for notice of opportunity for hearing when the agency proposes to refuse to approve a new drug application or to withdraw the approval of an application, do not apply in this situation. The agency stresses that the therapeutic equivalence evaluations are based on information already in FDA files as to the safety, effectiveness, and quality of approved drug products and as such are not new claims. Furthermore, the evaluations of therapeutic equivalence apply only to approved drug products and are based on their pharmaceutical equivalence, bioequivalence, labeling, and compliance with current good manufacturing practice regulations. Thus, the List does not constitute an agency action requiring a notice of opportunity for hearing under § 314.200(a).

12. One comment said that FDA's proposal is contrary to section 5 of the Federal Trade Commission (FTC) Act. The Federal Trade Commission has held that making an affirmative claim for a product without a "reasonable basis" for the claim is an unfair trade practice under section 5. A reasonable basis in the case of a drug product, according to FTC precedents, requires scientific studies, medical literature, or clinical experience. The comment said that FDA acknowledges the lack of such evidence by its reliance on the presumption that pharmaceutically equivalent drug products are also bioequivalent unless there exists contrary scientific evidence. The comment also noted that under the standards of "reasonable basis" there is a serious question whether FDA's representation that a particular drug is therapeutically equivalent to another drug would constitute an unfair trade practice if such representation were made by a drug manufacturer.

The FTC precedents referred to by the comment are not applicable to the labeling and advertising of prescription drugs. Nonetheless, FDA believes that its determinations of therapeutic equivalence do rest on a reasonable basis, including scientific studies, medical literature, and clinical experience. Part III(B) of the proposal explains that a therapeutic equivalence determination is based on the following scientific and regulatory foundations: (1) Pharmaceutical equivalence—drugs which contain identical amounts of the same active drug ingredient in the same dosage form, and which meet compendial or other applicable standards of identity, strength, quality, and purity; (2) bioequivalence—drugs not presenting a known or potential bioinequivalence problem, or, if such a problem is shown, the drugs meet an appropriate bioequivalence standard; and (3) controls to ensure consistency of quality in, and pharmaceutical and bioequivalency among, individual batches produced by all manufacturers, which includes the new drug approval and antibiotic certification processes, the batch certification process, good manufacturing practice regulations, and FDA's monitoring of the marketplace. In addition, an FDA evaluation of therapeutic equivalence refers to those drug products which meet the four general criteria listed in the response to comment 7 above. The scientific and regulatory foundations and the criteria described above involve the use of scientific studies, medical literature, and clinical experience. Accordingly, a reasonable basis does exist for FDA to make therapeutic equivalence determinations, and the contention that FDA acknowledges the lack of a reasonable basis for such determinations due to its reliance on a presumption that pharmaceutically equivalent drug products are also bioequivalent unless there exists contrary scientific evidence, ignores the basis for that presumption in scientific studies and clinical experience. As will be explained in the response to comment 18 below, scientific studies and clinical experience have shown that it is unnecessary to use human subjects and clinical resources to test a large number of drugs for which there is no evidence of bioavailability problems, or to reprove the safety and effectiveness

of an active ingredient which has already been established to be safe and effective.

13. One comment noted that the listed manufacturers are likely to use the therapeutic equivalence evaluations in their promotional materials. The comment argued, however, that citations to the List in advertising and sales information would violate principles in the prescription drug advertising regulations. For example, 21 CFR 202.1(e)(6)(iii) prohibits "literature references or quotations that are significantly more favorable to a drug than has been demonstrated by substantial evidence or substantial clinical experience." The comment argued that because many of the drug products at issue have been approved with less than the statute's mandate for "substantial evidence," the conclusions in the List must be based upon substantial clinical experience if they are to be cited in advertising as a basis for a claim of therapeutic equivalence. For newly approved imitative products, substantial clinical experience simply does not exist. In addition, the comment said that references to the List in advertising by the manufacturer of a newly approved imitative product would present "information from a study in a way that implied that the study represents larger or more general experience with the drug than it actually does." (21 CFR 202.1(e)(6)(v).) Finally, the comment said that use of the List in advertising would constitute an improper citation to "favorable data or conclusions from nonclinical studies of a drug, such as * * * in vitro, in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated." (21 CFR 202.1(e)(6)(vii))

The agency disagrees that the use of therapeutic equivalence evaluations in advertising would violate the prescription drug advertising regulations. FDA's basis for determining therapeutic equivalence does meet the substantial evidence test in § 202.1(e)(6)(iii), and does include studies which have clinical significance as stated in § 202.1(e)(6)(vii). In addition, § 202.1(e)(6)(v) is not violated because reference to therapeutic equivalence evaluations would not imply a broader experience with the drug than has actually occurred. As explained in the proposal, an evaluation of therapeutic equivalence applies only to approved prescription drug products that are pharmaceutically equivalent, bioequivalent, adequately labeled, and are manufactured in compliance with current good manufacturing practice. Other considerations in determining therapeutic equivalence include conformity with compendial or other standards of identity, strength, quality, and purity. Some of the mechanisms FDA uses to determine therapeutic equivalence are the new drug approval and antibiotic certification processes, the batch certification procedures, the good manufacturing practice regulations, and the agency's monitoring of the marketplace. FDA also disagrees with the comment that the phrases "literature * * * more favorable" and "favorable data or conclusions" are applicable to the agency's therapeutic equivalence evaluations. As explained in the response to comment 11 above, to the extent that the List sets forth FDA's evaluation of therapeutic equivalence, it contains FDA's advice to the public and to the States regarding an important public health matter. The evaluations do not constitute determinations that any products are in violation of the act or that any products are preferable to others. They are based on the application of certain criteria to information contained in FDA files to make these nonregulatory evaluations.

The agency notes, however, that it is now considering whether the use of therapeutic equivalence evaluations would be appropriate in prescription drug advertising or in prescription drug product labeling. When an agency policy is developed on these issues, it will be publicly announced.

14. One comment contended that the proposed therapeutic equivalence codes in the List are not uniformly favorable. For example, drug products coded "BX" are adverse findings which should be communicated to health professionals through the package insert. The comment further contended that the regulations governing supplemental new drug applications appear to require that drug product labeling be modified to reflect FDA equivalence findings, since 21 CFR 314.8(d)(2) requires the deletion "from package labeling, promotional labeling, and drug advertising of false, misleading, or unsupported indications for use or claims for effectiveness." The comment also said it may be that mere approval and labeling of a product with the generic name of the drug implies that all products containing the same active ingredient are equivalent. In some States, the comment noted, substitution of such products for their fully approved counterparts is lawful. Yet, the comment said, drug product labeling fails to advise physicians and pharmacists of the fact that these products are not therapeutically equivalent. This would cause the drug labeling to be misleading for failure to reveal a material fact (21 U.S.C. 321(n)) and would require correction under 21 CFR 314.8(d)(2). The comment concluded that the regulatory principles discussed above dramatize the inconsistency of the proposed List with the well-established principles under which the Federal Food, Drug, and Cosmetic Act is now administered.

The agency disagrees with the comment. First of all, the "BX" code is not an adverse finding regarding a particular drug product, but merely indicates that at the present time the agency has insufficient data to determine whether the product is therapeutically equivalent under the stated criteria. Neither the "BX" code nor any of the other therapeutic equivalence evaluations constitute determinations that a product is in violation of the act or that a product is preferable to others. They are nonregulatory evaluations based on the application of the four criteria for therapeutic equivalence (i.e., pharmaceutical equivalence, bioequivalence, adequacy of labeling, and current good manufacturing practice) to information already contained in FDA files concerning the drug products. Second, the agency disagrees that § 314.8(d)(2) would require drug product labeling to be modified to reflect FDA therapeutic equivalence findings. For reasons already explained in the proposal and in the responses to comments number 11 and 12 above, the therapeutic equivalence evaluations are not "false, misleading, or unsupported indications for use or claims for effectiveness." Third, as explained in response to comment 13 above, the agency is considering whether information concerning therapeutic equivalence evaluations should be used in prescription drug product labeling or advertising. Pending that consideration, the agency has not determined that information concerning therapeutic equivalence or therapeutic inequivalence is a material fact under 21 U.S.C. 321(n). However, since prescription drug product labeling and advertising does not presently include information concerning therapeutic equivalence evaluations, such evaluations are not directly relevant to drug product labeling because the labeling provides adequate information for the safe and effective use of the drug product. "Therapeutically equivalent drug products" refers to drug products which are otherwise safe and effective and which can be expected, in the judgment of FDA, to have equivalent therapeutic effect and equivalent

potential for adverse effects when used under the conditions set forth in their labeling.

15. Several comments stated the belief that the List would be promoting the interchangeability of drugs. One of these comments said that by publishing the List, FDA will in effect become an insurer of drug interchangeability and therapeutic equivalency in the United States. The comment explained that the implications of this are significant. For example, any physician or pharmacist who is sued for malpractice because of the unintended result of a prescription drug product could rely in defense on the List. Another comment said that FDA should assume all medical and legal responsibility for drug substitutions that the physician and pharmacist carry out. A third comment said that States would rely on the List as an "implied guarantee" of the interchangeability of drugs, and that this would raise questions concerning Federal and State legal liability for the content of the List.

It is not FDA's intent to become an "insurer of drug interchangeability," nor is it the agency's intent to assume all responsibility for drug product substitution by physicians and pharmacists. As pointed out in the proposal, FDA believes that drug products that are therapeutically equivalent are not necessarily interchangeable in all instances. Because such products may still vary, for example, in color, shape, taste, or packaging, patients may not perceive them as identical or equally acceptable. FDA makes no judgment as to whether different drug products are substitutable or interchangeable for use by a particular patient; rather, this judgment rests with practitioners who, in prescribing and dispensing drug products, should consider the unique characteristics, needs, or problems of the patient. Regarding the comment concerning physician or pharmacist malpractice suits, an FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional duty to prescribe and dispense drug products with due care to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate. Also, pharmacists must be familiar, for example, with the expiration times and labeling conditions for storage, particularly for reconstituted products, to ensure that patients are properly advised when one product is substituted for another.

16. Another comment, noting that FDA is proposing to amend 21 CFR 20.177, which provides that certain computer printouts be made available for public inspection at FDA, said that the computer printouts referred to in this section include information on new drugs and abbreviated new drug applications, approval status, and other information on IND's and NDA's. In none of these, the comment said, does FDA make any additional administrative determinations. The comment argued that the List, however, which is proposed to be part of this same section, would include evaluations of therapeutic equivalence. The comment said that because these are not part of the IND or NDA approval process, they do not belong in this section of the regulations. The comment concluded that FDA does not distinguish between its authority to disclose, on the one hand, information readily available in agency records and, on the other hand, new information based on complex medical and scientific determinations of therapeutic equivalence.

FDA advises, as stated in the proposal (at p. 2937), that it is amending § 20.117 in conjunction with the List only to give the public a point of reference reflecting the availability of the List. Because the List is informational and advisory in nature, the agency believes that it is best identified in the regulations describing FDA records and information that are available to the public. Contrary to what is said in the comment, FDA believes that the List is relevant to information on NDA's and ANDA's. The List includes prescription drug products which FDA has had the authority and opportuntiy to evaluate and approve for safety and effectiveness. It also includes therapeutic equivalency determinations of these approved drug products based on the general criteria explained above.

17. One comment said that States will interpret the List as a Federal directive and not merely as FDA assistance to the States. The comment said that such a directive would be beyond FDA's legal authority.

The agency disagrees that States will interpret the List as a Federal directive. The legal status of the List was clearly explained in the **Federal Register** proposal (at p. 2939). Further, the proposal explained that one reason FDA is publishing the List is in response to requests from several States for assistance in developing their drug product selection legislation. Pharmacies, hospitals, States, and private and public institutions and organizations continue to ask FDA to share its broad knowledge of the safety and effectiveness and quality of drug products, so that they can continue to carry out their duties to protect and promote the public health, both in providing health care services safely and with efficiency and cost-effectiveness, and in advising physicians and pharmacists on drug product selection.

III. Therapeutic Equivalence

18. Several comments questioned FDA's presumption that pharmaceutically equivalent drug products are also bioequivalent unless there is scientific evidence to the contrary. Some of the comments said that the agency's presumption is not supported by scientific data and does not represent sound scientific reasoning. The comments contended that pharmaceutical equivalence and therapeutic equivalence should be determined on a case-by-case basis. Other comments cited examples of products to show the dangers in presuming that pharmaceutically equivalent drug products are also bioequivalent in the absence of evidence to the contrary, and said FDA's approach is premature because additional problems may not emerge until there is more experience with product interchange and more multisource products.

FDA disagrees with the criticism directed at its conclusion that pharmaceutically equivalent drug products are also bioequivalent unless there is scientific evidence to the contrary. FDA is of the opinion that only where scientific evidence demonstrates a known or potential problem of bioinequivalence should a manufacturer be required to establish that its product is bioequivalent to a reference product, which generally is the pharmaceutically equivalent product marketed by the holder of the original new drug application. In such a situation, individual products are presumed not to be bioequivalent until proven otherwise by adequate scientific studies.

Since the early identification of bioinequivalence problems, FDA has sought to ensure the bioequivalence of pharmaceutically equivalent drug products. The agency has undertaken two parallel activities: (1) The development of requirements for bioavailability testing and for demonstrating bioequivalence (now codified in 21 CFR Part 320), and (2) in anticipation of such requirements, a review of the evidence of bioavailability and bioequivalence in ANDA's for those pharmaceutically equivalent drug

products for which evidence of a bioinequivalence problem exists. This second activity has functioned well for the last 8 years and has provided considerable bioequivalence data and information from ANDA submissions. For these products there is a reliable basis for determining the bioequivalence of specific pharmaceutically equivalent drug products. In addition, much information has been obtained from FDA-supported research and from the scientific literature.

Because many of the issues raised by the comments were debated during the development of the above programs, FDA does not believe it is necessary to respond in detail at this time. The proposal (at pp. 2940–2943) discusses such earlier debates. FDA remains convinced that only where scientific evidence demonstrates a known or potential problem of bioinequivalence should a manufacturer be required to establish that its product is bioequivalent to a reference product. FDA believes that among the drugs that are currently marketed by more than one supplier, those drugs having known or potential bioinequivalence problems have now mostly been identified. For the remainder, bioequivalence can be presumed on the basis of pharmaceutical equivalence. As the Drug Bioequivalence Study Panel of the Office of Technology Assessment (OTA) concluded in 1974: "It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic importance to toxic concentration in blood, and certain pharmaceutical characteristics." FDA believes it is neither in the interest of the public health nor a productive use of the nation's scarce research resources to require costly duplication of tests. A regulatory system that requires such duplicative testing is wasteful, anticompetitive, scientifically unsound, and ethically dubious.

19. One comment questioned FDA's presumption that compliance with dissolution standards ensures bioequivalence and, therefore, therapeutic equivalence. The comment said that in the current state of the art, the true test of effectiveness or equivalence of a drug product is the controlled clinical trials or, at a minimum, measurement of blood levels in man compared with those of an accepted reference product. Yet, the comment said, many products that were presumed to be equivalent to pioneer products in FDA's List have been subjected to neither test.

The agency believes that compliance with dissolution standards does help to ensure bioequivalence and therapeutic equivalence. The results of in vitro dissolution testing are a useful and reliable indication of uniformity in manufacturing a product, and the rate of dissolution does influence the bioavailability of the drug. The agency disagrees, however, that in vivo tests, clinical trials, or blood level determinations are required for every drug product to show effectiveness or equivalence. As explained in the response to comment 18 above, a manufacturer should be required to establish that its product is bioequivalent to a reference product only where scientific evidence demonstrates a known or potential problem of bioinequivalence, and, among the drugs that are currently marketed by more than one supplier, most drugs having bioinequivalence problems have now been identified. Thus, there is little or no scientific justification for involving human subjects and huge clinical resources to test a large number of drugs for which there is no evidence of bioavailability problems, or to reprove the safety and efficacy of an active ingredient which is already firmly established as safe and effective. In addition, unnecessary human testing cannot be ethically justified. It should be noted that in vivo tests are imposed for drugs having documented or potential bioequivalence problems.

20. One comment said the net number of drugs included in the List that are realistically eligible for source selection by the pharmacist at retail is only 134, or about 14 percent of the entire List. The comment noted that over half of these items are designated as "AB", meaning that FDA at some point thought they presented questions of bioequivalence and sought additional data from the manufacturers. These figures are significant, the comment argued, because FDA has said that relatively few drugs have inequivalence problems. In fact, the comment argued, the agency's own list of potential problem drugs constitutes more than half of the multisource market represented in the List. The comment also said that since so many multiple-source drugs are designated as "AB", FDA should make available the information that prompted a conclusion that these drugs are equivalent.

The agency advises that the purpose of the Approved Prescription Drug Products List is to provide a list of prescription drug products that FDA has had the authority and opportunity to evaluate for safety and effectiveness. In addition, the List contains evaluations of therapeutic equivalence for these approved drug products. In developing the List, FDA evaluated for therapeutic equivalence only multisource drug products, i.e., those pharmaceutical equivalents available from more than one manufacturer, since those are the only products that are eligible for source selection by health-care professionals. As stated in the response to the first two comments in this part of the preamble, FDA believes that among multisource drugs, most drugs having known or potential bioinequivalence problems have now been identified. For the remainder, bioequivalence can be presumed on the basis of pharmaceutical equivalence. In publishing the List, FDA is not claiming that all drug products are therapeutically equivalent or that all products are bioequivalent. As indicated by the comment, many drug products in the List are coded as therapeutically inequivalent, and many of these are so designated because of bioinequivalence problems. FDA's contention is that it has studied and is continuing to study bioavailability/bioequivalency among the nation's drugs and, based on information available to the agency, it is now able to evaluate the therapeutic equivalency of all multiple-source drug products that the agency has approved through the new drug approval process or the antibiotic certification process. In addition, FDA will revise these evaluations whenever warranted by new information, including bioavailability/bioequivalency data.

Regarding the comment that FDA should make available the information upon which it based its conclusion that "AB" drugs are therapeutically equivalent, the agency believes that the List, the preamble to the proposal, and this preamble to the final rule provide sufficient explanation and background for FDA's determinations of therapeutic equivalence. The agency does not believe it is either necessary or practical to include in the List the complete data that were reviewed by FDA scientists to determine the therapeutic equivalency of drug products on the List.

21. One comment said that because the List names 54 more drugs as having bioequivalence concerns than were named in the 1976 list of drug products with bioavailability problems, popularly known as the "Blue Book," inequivalence should be assumed in the absence of proof to the contrary. The

comment also noted that 11 products previously listed as "approved" in that publication are excluded from the List.

The agency disagrees that this increase in the number of drug products listed as having bioequivalence concerns is due entirely to previously unanticipated bioequivalence problems. The publication referred to (HEW Publication No. FDA/76–3009; see the **Federal Register** of February 5, 1976 (41 FR 5339)) included a list of drug products with known or suspected problems of bioinequivalence which were subject to approved new drug applications. That list excluded post-1962 drug products, DESI drugs requiring a full NDA as a basis of approval, controlled-release and enteric-coated products, and antibiotic products. Of the 54 drugs mentioned by the comment as being included in the 1979 List but not in the 1976 list, 24 were antibiotics which were excluded because oral antibiotics had undergone in vivo testing for approval and certification; 12 were post-1962 drugs; one (phenytoin) was reported missing from the 1976 list but actually was included; one (chlorotrianisene) was incorrectly coded as "BP" in 1979 List and should have been coded as "AA"; two were DESI drugs requiring a full NDA and thereby excluded from the 1976 list; and six were found inequivalent due to reasons other than bioequivalence. This leaves the following eight bioavailability-problem drugs which were included in the 1979 list but were inadvertently overlooked in compiling the 1976 list: Colchicine-probenecid (BP), medroxyprogesterone acetate (BP), prednisolone acetate (BP), testosterone (BP), fluoxymesterone (BP), amitriptyline (AB) and (BP), sulfamethoxazole (AB) and (BP), sulfamethizole (AB).

Regarding the comment which noted that 11 drugs were included in the 1976 list as approved but are excluded in the 1979 List, the agency advises that the marketing of most of these products has been discontinued by their manufacturers. Two of these 11 drugs, digitoxin and digoxin, are not included in the 1979 List and are specifically mentioned in the 1976 list as not requiring an NDA because of their "old drug" status. In summary, the 11 multiple-source compounds which are identified in the 1976 list as being approved, but which are not included in the 1979 List are: Aminosalicylic acid tablets, bendoflumethiazide tablets, and paramethasone acetate tablets—included in the 1979 list as single source drugs; potassium aminosalicylate powder and tablets—the powder is coded "AA" in the List, and the tablets are now single source; digoxin tablets and digitoxin tablets—the injectable form is on the list, and the tablet form is not the subject of an approved application and is therefore excluded from the 1979 List; benzoylpas calcium powder, calcium aminosalicylate granules and tablets, dienestrol tablets, sulfamethoxypridazine tablets, and sulfamethoxypridazine acetyl oral suspension—all have been discontinued by their manufacturer.

22. Another comment said the definition of "pharmaceutical equivalents" should require that the products contain the same inactive ingredients or that they be produced by the same manufacturing methodology or technique. The comment explained that manufacturing involves the process and the technique of production as well as the selection of so-called inactive ingredients to achieve the predetermined objective of the dosage form. Relatively minor alterations of any of these elements can influence the therapeutic effect of the product. One of the examples of this given by the comment is that magnesium stearate is on the generally recognized as safe (GRAS) list as a safe ingredient; however, when inappropriately used in a product formulation it can totally prevent absorption of a drug entity and ultimately lead to therapeutic failure. The analysis for safety is not sufficient to assume therapeutic equivalence. The comment also noted that FDA acknowledged in the definition of bioavailability that variations in inactive ingredients or manufacturing methodology or technique can result in variations in product performance.

Although FDA agrees with many points in this comment, the agency's experience with reviewing inactive ingredients does not support the statement that it is necessary and appropriate for "pharmaceutical equivalents" to contain the same inactive ingredients or to be produced under the same manufacturing method or technique. Inactive ingredients and manufacturing methodology are extremely important. Through the new drug approval process, FDA has the opportunity to review the proposed formulation and manufacturing procedures. The fact that they are not identical from manufacturer to manufacturer is one of the fundamental reasons why FDA has limited the List of drugs to "approved" drug products. The agency reviews inactive ingredients through a variety of mechanisms including the evaluation of individual inactive ingredients to ensure safety and the review of formulation information in new drug applications to ensure that appropriate ingredients are used. In addition, the agency imposes bioequivalence study requirements on drugs where there is reason to believe different formulations (of inactive ingredients) would pose bioequivalence problems.

23. One commenter said that during his service on the USP Committee of Revision the most serious problems encountered were those of FDA's concern with violations by substitution of potent medicaments with lower-cost, life-endangering substances that were both chemically and pharmaceutically equivalent, and in a sense even bioequivalent. Two examples of this substitution were: (1) The substitution of Cyanocobalamin (vitamin B^{12}) with an "equivalent" amount of cobalamin concentrate in high-potency injections which, because of protein and other impurities in the concentrate, produced shock in the patient and then death; (2) the substitution of reserpine with an "equivalent" amount of Rauwolfia extract, which produced side effects more serious than those of the potent but useful reserpine.

The agency believes that the comment has confused two terms that were defined in the proposal. The examples cited by the comment do not fit the definiton of "pharmaceutical equivalents." Cyanocobalamin and cobalamin concentrate as well as reserpine and Rauwolfia extract are not drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety in identical dosage forms. Rather, they are "pharmaceutical alternatives," i.e., drug products that contain the identical therapeutic moiety, or its precusor, but not necessarily in the same amount or dosage form or as the same salt or ester. FDA does not evaluate the therapeutic equivalence of pharmaceutical alternatives.

24. One comment questioned FDA's position that therapeutically equivalent drug products may vary in certain respects such as color, taste, shape, or packaging without affecting their equivalence. The comment argued that each of these characteristics, if changed in an NDA-approved product, would require a supplement to the NDA supported by bioequivalence and stability data. The comment noted that stability is crucial to the integrity of the drug entity and to the release characteristics of the drug from the drug product. In addition, changes in disintegration and/or dissolution rate can adversely effect the bioavailability

of the product. The comment said it is essential to define the ways in which drug products vary because these variations may directly affect compliance with therapeutic regimens.

The agency notes that the proposal explained that drug products that are therapeutically equivalent may still vary in characteristics such as color, shape, taste, or packaging. Because of this, patients may not perceive such drug products as identical or equally acceptable and, thus, it cannot be said that they are substitutable or interchangeable in all cases. FDA believes that in such cases the practitioner, in prescribing and dispensing drug products, should consider the unique characteristics, needs, or problems of the patients. However, so long as there exists this professional regard for the individual patient, FDA believes that if one therapeutically equivalent drug product is substituted for another, there is no substantial reason to believe that the patient will receive a drug product that is different in terms of the therapeutic effect intended.

FDA agrees with the comment that improper packaging may affect drug stability and, thus, the bioequivalence of drug products. This is taken into account in the NDA and ANDA approval process. In addition, supplemental requirements for these changes and whether bioavailability data or stability data are required in the supplement are covered in §§ 314.8 and 320.21 of the regulations.

25. One comment disagreed with FDA's statement that internal manufacturing standards used to provide greater patient convenience or patient acceptance of a drug product do not relate to the safety and effectiveness of the drug product but are considered pharmaceutical elegance. The comment argued that patient compliance is often related to patient convenience and the acceptance of a drug product and that patient compliance is directly related to the actual safety and effectiveness experienced with any drug therapy. The comment said that FDA has not sufficiently recognized the importance of patient compliance in the actual effectiveness of ingestible products, especially in light of FDA's recent reversal of its position that fasting versus with-meals labeling differences between E-mycin and the generic erythromycin does not defer the establishment of therapeutic equivalence evaluations for maximum allowable cost (MAC) purposes. Another comment disagreed with FDA's statement that manufacturers who adopt specifications beyond those needed to reasonably ensure drug product quality do so for the purpose of elevating product "elegance" and that such additional standards do not necessarily produce a "better" product. The comment cited FDA's argument in the *Lannett* case, i.e., "Everyone is aware that a dozen different chefs can use the same ingredients, the same recipe, and employ the same enthusiasm, but produce a dozen different versions of what should be the same meal. No less is true of drugs, particularly drugs which present bioavailability problems * * * Variations in manufacturing processes, equipment, storage, and inactive ingredients may and do give rise to dissimilarities among products * * *." The comment contended that FDA's argument in *Lannett* is compelling and should not be ignored at this time.

The agency agrees that patient compliance is often related to patient convenience and the patient's overall acceptance of a drug product. In addition, the degree to which a patient complies with the prescribed drug therapy will obviously be a factor in how effective that drug product will be. The agency also believes, however, that bioequivalent drug products which have standards beyond those required to establish their safety and effectiveness and bioavailability may have distinguishable differences in appearance, taste, and so on. As discussed in the proposal (at p. 2940), these differences may result in one product being preferred over another, but it would not be a "better" product in the sense that it is more effective or safe.

The agency believes that the comment is incorrect in contending that a MAC was not established for erythromycin-base tablets because of a recognizable difference in labeling, and that this could affect patient compliance and product performance. An MAC was initially recommended by FDA because all manufacturers of these dosage forms demonstrated the bioavailability/bioequivalency of their product through appropriate in-vivo studies. The agency reversed its position after a review of data submitted by the Upjohn Co. which showed that its enteric-coated erythromycin-base product provided significantly higher blood levels when administered in the presence of food than under fasting conditions. Perhaps the comment was referring to erythromycin stearate tablets. As the agency noted in the preface to the List, some firms were able to show that their product performed satisfactorily when administered shortly before meals and therefore was labeled to reflect that information. However, erythromycin stearate is much more adversely affected by food than is erythromycin-base enteric-coated drug products and, when administered shortly after food intake, is marginally acceptable. On this basis, FDA stated in the preface to the List that optimal product performance is achieved when erythromycin stearate is given under fasting conditions, and recommended that all products be so administered. Under these conditions, all products have been demonstrated to be bioequivalent.

FDA also disagrees with the comment's reference to the *Lannett* argument. In *Lannett*, the agency was concerned with firms producing a product without an approved new drug application. The comment apparently interpreted the quoted portion of the *Lannett* argument to mean that the agency does not believe that manufacturers under any circumstances can produce an equivalent drug product even when using the same ingredients. That interpretation is incorrect. The new drug application system is designed to ensure safe and effective drugs as well as comparable drug product performance, regardless of differences in inactive ingredients. Standards beyond those needed for safety, effectiveness, and bioavailability go to that product's pharmaceutical elegance and quality.

26. One comment said that FDA's position on the value of compendial standards in ensuring multisource product equivalence is inconsistent with that argued in the *Lannett* case. In *Lannett*, FDA stated that "only specially designed tests on each manufacturer's product rather than standards set forth in recognized compendia" can determine whether a me-too drug product is bioequivalent to the pioneer drug. However, in support of the 1979 List, FDA stated: "For these reasons, it is appropriate to conclude that current compendial and antibiotic standards and similar standards in new drug applications provide a reasonable basis for evaluating whether two or more drug products are pharmaceutically equivalent and thus may be therapeutically equivalent."

The agency has not been inconsistent with regard to the importance of compendial standards. The position of the manufacturer in the *Lannett* case was that its products met compendial standards and that nothing more was needed to ensure product quality and performance. The agency's position is that compendial requirements alone will

not ensure acceptable bioequivalence performance and that application standards are therefore essential to ensure bioequivalence. Where bioequivalence is not an issue, compendial requirements are important in ensuring product quality.

27. One comment disagreed with FDA's statement that the compendia have made significant improvements since the 1974 OTA report (e.g., the adoption of dissolution standards). The comment stated that pharmaceutical scientists have shown that much remains to be done with equipment and procedures before reproducible dissolution standards can be established.

The agency believes that significant improvements have been made in the compendia since the 1974 OTA report. One of the more notable accomplishments is that 25 dissolution standards were added to the *U.S. Pharmacopeia* (USP) (from 7 in 1970 to 32 in 1975), and 4 were added to the *National Formulary* (NF) (from 5 in 1970 to 9 in 1975). A somewhat wider application of dissolution requirements was made in the 1980 edition of the USP/NF. The agency recognizes that the reproducibility of dissolution testing has posed difficulties with some drugs. However, extensive assistance for dissolution testing and training programs for the paddle method provided by the agency's National Center for Drug Analysis have done much to improve this situation. The agency believes that the USP has been moving forward by developing improved equipment specifications and calibrators that are more precise and better defined than those previously used.

28. Another comment disagreed with the statement in the proposal that individual manufacturers who use standards exceeding those of the compendia refuse to make such standards public. The comment contended that improvement in test procedures developed by innovative companies are often used by innovators before their general use simply because of the substantial "compendial lag" that exists from the time a new test is submitted until it becomes official in the compendia.

Consistent with the statement in the proposal, FDA is aware of examples where manufacturers have failed to provide to the USP all of the specifications they use for producing a drug substance or product. However, the agency recognizes that improved test procedures may be used by innovators before their general use or before their adoption by the compendia. The necessary validation and review procedures that must be accomplished before new test procedures can be adopted officially and required of all manufacturers of a drug product require considerable time.

29. One comment stated that the proposed therapeutic equivalence evaluations incorrectly assume that certain drug products approved on the basis of less-than-full NDA's will perform in the same fashion as their fully approved counterparts.

The agency believes that the approval of drug products through the ANDA process is a valid basis for therapeutic equivalence determinations. The agency disagrees with the argument that the ANDA approval process is less demanding than the NDA approval process, and that product quality is less reliable among drug products covered by an approved ANDA. As explained in the proposal, an ANDA is authorized instead of a full NDA only after a decision has been made through the DESI review process that further clinical studies demonstrating the safety and effectiveness of the product are unnecessary. FDA requires that the person submitting an ANDA for a product demonstrate that the product is bioequivalent to the innovator's product, or in certain cases to a reference standard, unless the person submitting the ANDA can demonstrate that the bioavailability of its product is self-evident, or the agency decides that bioavailability is unimportant to the achievement of the product's intended uses. Because the safety and effectiveness of an ANDA's drug was previously demonstrated, and because of the bioequivalence requirement, it is clear that products approved through the ANDA process will perform in the same fashion as their counterparts approved through the full NDA process. Although some products were approved through the ANDA process before the bioequivalence requirements were implemented, FDA believes that it would be unnecessary and wasteful to now require proof of bioequivalence of all these products when there has been no documented evidence of or potential for bioinequivalence. For those products that do present known or potential bioequivalence problems, FDA can require bioavailability data at any time. FDA will not evaluate as therapeutically equivalent any products with a known or potential bioequivalence problem.

30. One comment stated that opinions vary on the inferences to be drawn from the existence of an approved ANDA based on the requirements for approval, and suggested that additional information is needed to help evaluate the strength of the inferences FDA draws from mere ANDA approval. Because the ANDA procedure makes little or no contribution to assurances about equivalence, the comment stated, the agency has an obligation to more precisely inform the public about what products on its List actually have bioavailability data on record. The comment said that FDA should supply a list of products showing (a) those for which a bioequivalence requirement was imposed by FDA, (b) those ANDA's which included in vivo bioavailability data, and (c) those for which FDA imposed a bioavailability requirement that was subsequently deferred. In addition, FDA should make public (1) the statistics relating to chemical inequivalence uncovered by the agency's program which tests categories of drugs on the basis of therapeutic importance, volume of usage, past quality problems, and other parameters, (2) the frequency and percentage of bioequivalence problems uncovered through FDA-funded clinical studies, and (3) any data the agency has to support its position that there are very few bioinequivalence problems among marketed multi-source products.

The agency believes, as explained in the respose to comment 29 above, that the ANDA procedure does contribute to assurances of therapeutic equivalence. In addition, the List provides the information called for by this comment. In regard to item (a) above, the List identifies all active ingredients and dosage forms that the agency believes pose actual or potential bioequivalence problems and identifies which firms have completed bioequivalence studies for these drug products. In regard to item (b) above, the List provides information as to which new drug applications have been accompanied by in vivo bioequivalence studies for those drug products. In regard to item (c) above, the List identifies those situations where the agency believes that a firm should demonstrate the bioequivalence of its products but has not yet done so. The information that the comment suggests that FDA make public, i.e., items (1), (2) and (3) above, are available from various sources. The data relating to chemical inequivalence referred to under item (1) of the comment is already available to the public under the Freedom of Information Act. The frequency and percentage of bioequivalence problems uncovered through FDA-funded studies has been publicized through publications in newsletters and scientific journals by the investigators who performed these studies. The data on which the agency

based its conclusions regarding the extent of bioinequivalence problems among marketed multisource products are referred to at length in the proposal (at pp. 2941–2943).

31. In the proposal, FDA explained that it assures the quality of marketed generic drug products through its authority to require premarketing approval of an ANDA that contains information about the manufacturing processes, ingredients, and labeling to be used by each firm marketing the drug. However, one comment contended that the *Lannett* decision has shown this assumption to be erroneous because FDA conceded that each of the drugs involved in that case was generally recognized as safe and effective as a generic entity, but the agency maintained that the individual product formulations were new drugs for which prior approval was required. The comment noted that the court rejected FDA's argument, and held that *Lannett's* products were not new drugs within the meaning of the act. The comment said that the agency could not compel *Lannett* to submit manufacturing and quality data for FDA's review and approval before it commenced marketing. The comment concluded that, under the *Lannett* holding, FDA can no longer effectively require that persons wishing to introduce generic products into the market first obtain approval of their manufacturing and quality control capabilities through the ANDA process.

The agency disagrees that, under the *Lannett* holding, it can no longer effectively require that persons wishing to introduce generic products into the market first obtain approval through the ANDA process. FDA continues to maintain that the language in *Lannett* regarding this issue was "dicta," and that the Court of Appeals for the Third Circuit held only that the district court incorrectly concluded that *Lannett* had not waived its right to an administrative hearing on the proper classification of its drugs. The Solicitor General decided not to seek certiorari to the U.S. Supreme Court in *Lannett* because such a petition could seek review only of the actual decision of the court of appeals, with which FDA does not disagree, rather than a review of the "dicta" in the court's opinion, with which FDA does disagree.

Subsequent to the *Lannett* decision, a different appellate court strongly supported FDA's position that generic copies of previously approved drugs are subject to premarketing approval. *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, Nos. 79–6226, 79–6185 (2d Cir. July 29, 1980). FDA is continuing to require premarketing approval for generic drug products and believes that, if needed, the Supreme Court will review this issue. It should also be noted that only those drug products for which FDA has had the authority and opportunity to evaluate for safety, effectiveness, and quality are included in the List. Thus, in light of *Lannett*, the List is especially important because it enables physicians and pharmacists to identify FDA-approved drug products for selection.

32. Two comments said that one of the most important criteria established by FDA in judging whether or not two products can be considered equivalent in the manufacturer's record of compliance with FDA's Current Good Manufacturing Practice (CGMP) regulations. The comments said, however, that without accurate manufacturer compliance information, the List does not assure prospective users that the sources of supply listed are in fact performing competently. The comments pointed out that the appearance of a product on the List under the code "AA" or "AB" implies that the manufacturer is in compliance with CGMP regulations. But the comments said that an examination of the public record on the performance of suppliers whose names and products are listed in the New York generic drug product list does not support any general endorsement of the quality of listed firms. In some cases, the comments noted, the record shows major compliance failures that are recent and unresolved, despite the inclusion of both the company and the products inspected in the FDA List. The comments cited the following examples as taken from actual FDA inspection reports of Quality Assurance Profiles: Inspections at two of a firm's establishments revealed serious violations of CGMP requirements from August to September, 1978. On January 5, 1979, FDA issued its List including 10 of the firm's drugs. Four of those 10 had specifically been identified as not conforming to CGMP regulations. The comments said that on January 30, 1979, FDA issued to the firm a regulatory letter alleging that the August to September inspection findings were serious violations which, if not corrected, warranted further regulatory sanctions. The comments concluded that the FDA record demonstrated that the manufacturer was not in compliance with CGMP regulations when its products were placed on the List. The comments also said that there is at least one firm mentioned in the FDA List whose products were recently excluded by the New Jersey Drug Utilization Review Council from the State's generic drug product list. The firm's poor record of compliance with CGMP regulations was cited as the reason for the exclusion.

The agency agrees that compliance with CGMP regulations is necessary to assure batch-to-batch consistency in drug product quality and believes it has been successfully enforcing the CGMP regulations. Also, the agency substantively improved the CGMP regulations as published in the **Federal Register** of September 29, 1978. However, as indicated in the preface to the List, from time to time approved products—whether brand name or generic—may violate one or more requirements of the act. In such cases, the agency will initiate appropriate enforcement action to remove the violative product from the market. If the problem leading to the violation continues, FDA will undertake additional steps to eliminate the risk. Such regulatory action, however, is independent of the inclusion of products in the List. The sole criterion for inclusion of a marketed product in the List is its being the subject of an approved application. Marketed products will not be removed from the List until completion of FDA proceedings to withdraw approval of the product under section 505 or 507 of the act, as applicable. FDA believes that retention of a violative product on the List will not have any adverse health consequences because other legal procedures are available to the agency to prevent actual marketing of violative products.

It should also be noted that when there is a change in the information contained in FDA files concerning a multiple-source drug product that is on the List, there exists the potential that the drug product will no longer meet the criteria for therapeutic equivalence as initially evaluated. In this instance, FDA will reevaluate the drug's therapeutic equivalency by applying the current information to the criteria for therapeutic equivalence. If the reevaluation reveals that the listed therapeutic equivalence evaluation is no longer accurate, the evaluation will be revised accordingly.

33. FDA stated in the proposal that the latest revision of CGMP regulations would assure a high degree of batch-to-batch consistency of drug product quality. A comment contended that the extent to which CGMP regulations contribute to product uniformity among multiple sources is directly proportional to the uniformity of enforcement by

FDA's inspection programs. The comment claimed that inspection standards and frequency of inspection vary among different categories of manufacturers, and FDA inspectors vary considerably in their abilities to evaluate manufacturing and quality control standards. The comment also said that significant differences appear to exist in the enforcement practice of FDA's district offices. Another comment stated that CGMP regulations provide "minimum standards" and that a requirement of meeting minimum standards does not ensure the equivalence of multisource manufactured products.

FDA is aware of the need to achieve uniform enforcement not only of the CGMP regulations but in all of its compliance activities. The agency strives to meet this goal through a number of programs. For example, FDA has comprehensive training programs administered both nationally and regionally, such as its basic and advanced drug schools. These programs are designed to enhance the expertise of field inspectional staff and to promote a uniform approach to CGMP inspections. Uniformity is also promoted through the use, by headquarters and field personnel, of inspectional, compliance, and administrative programs in such staff manuals as the *Investigator Operations Manual,* the *FDA Compliance Programs Manual,* and the *Compliance Policy Guide Manual.* Uniform interpretation/application of the CGMP regulations is also promoted through headquarters-field communications, including periodic meetings of the staffs of the field districts and the Bureau of Drugs. In addition, the agency has a centralized review and approval process for all its regulatory actions.

The agency acknowledges that perfect uniformity of enforcement, as apparently envisioned by the commenter, is complicated by two unavoidable factors. First, no two cases of noncompliance with CGMP's are exactly alike. The type of response FDA may consider could therefore vary somewhat from case to case, and is based on such considerations as the severity and number of violations, the potential impact on drug product quality, safety, and effectiveness, the potential for a health hazard, and the effectiveness and promptness of any corrective measures. These considerations necessitate a certain amount of individual judgment, which is the second factor. Within the framework of established policies and procedures a certain degree of individual judgment must be exercised, from the observations of the field investigators to district managers to headquarters officials. The agency is convinced, however, that multiple levels of review incorporated in its compliance procedures are sufficient to counter any negative impact this factor may have on achieving the greatest possible degree of uniform enforcement. These multiple levels of review include the review of all proposed significant regulatory actions by the Bureau of Drugs, Office of the Commissioner, and the General Counsel before referral to the Department of Justice.

Regarding the frequency of FDA inspections, the agency acknowledges that some drug firms may, in fact, be inspected more often than others. Although the Federal Food, Drug, and Cosmetic Act requires at least biennial inspections of drug manufacturers, more frequent inspections may be made for a variety of reasons. For example, a firm's state of compliance may necessitate more frequent inspections to ensure that CGMP violations are corrected. The agency wishes to clarify, however, that not all FDA inspections involve comprehensive CGMP evaluations. For example, limited inspections may be conducted to obtain specific product stability data, to investigate consumer complaints, to collect samples and review production records under national surveillance programs, or to inspect drug products offered under contract to Federal agencies under the Government-Wide Quality Assurance Program. The agency believes that these inspections do not hinder uniform enforcement. In fact, uniform enforcement could be hampered if all firms were inspected with equal regularity, regardless of the circumstances.

Regarding the comment that the CGMP regulations constitute only the minimum current good manufacturing practice, the agency believes that when these standards are followed they provide a high degree of assurance of drug product quality. The agency wishes to emphasize, however, that compliance with CGMP regulations is only one of the factors which determines a finding of therapeutic equivalence. Pharmaceutical equivalence, bioequivalence, and adequacy of labeling are additional factors that are considered in determining a therapeutic equivalence evaluation.

34. One comment disagreed with FDA's contention that under section 507 of the act the monitoring of drug product manufacturing processes ensures batch-to-batch uniformity of individual product entities. The comment cited FDA as saying that from January 1974 through October 1978, 20,000 batches were submitted with the rejection rate averaging less than one-half of 1 percent. The comment said that FDA's argument in this area is misleading, and that antibiotic batch certification requires only a series of in vitro tests which, at best, ensure chemical purity, potency, and unit-to-unit dosage form chemical content. The comment said there is documented evidence of bioinequivalence of marketed products that have passed all FDA batch certification requirements (for example tetracycline, oxytetracycline, and digoxin). The fact that the rejection rate of antibiotic batches has averaged less than one-half of 1 percent for more than 4 years, the comment said, is hardly compelling evidence upon which to assess the relativity of batch certification to therapeutic equivalence. The comment said that the only conclusion which may be drawn from these data is that there is agreement between a particular manufacturer's assay and the assay of FDA's certification laboratory.

The agency believes that the antibiotic batch certification process does help to ensure batch-to-batch uniformity of antibiotic drug products. Generally, antibiotic batch certification requires a series of in vitro tests, and, at times, biological tests, to ensure chemical purity, potency, and unit-to-unit dosage form chemical content. When FDA becomes aware of a bioinequivalence problem with an antibiotic, it may require that the product meet dissolution test standards. The agency has already developed such required certification standards for tetracycline and oxytetracycline. When a bioinequivalence problem is detected, a dissolution standard is developed using a product for which FDA has clinical evidence of safety and effectiveness and blood level information. The dissolution test is then added to the monograph as a requirement for certification. It should be noted that in addition to the antibiotic batch certification process, FDA uses other mechanisms to control batch-to-batch consistency, namely, current good manufacturing practice regulations and FDA's monitoring of the drug supply in the marketplace.

35. The criteria for pharmaceutical equivalents include the requirement that the products "meet compendial or other applicable standards of identity, strength, quality, and purity." Two comments expressed the view that although FDA monitors marketed drug

products through its analytical laboratories and its field surveillance, it cannot assure the public that all products meet the applicable standards. The comments said recalls of drug products represent failures of the quality assurance system, and that in many cases those products have been used for patient care before the deficiency comes to the attention of the manufacturer or FDA. The comment noted that the *FDA Quarterly Reports* said that approximately 70 percent of the domestic human drugs examined and classified by FDA are found to be in compliance. Since a significant portion of the marketed drug products does not comply with regulatory requirements, the comment concluded, an assumption of therapeutic equivalence is unwarranted.

FDA is confident that drug products found to be pharmaceutically equivalent and bioequivalent will remain so and thus may be evaluated as therapeutically equivalent. In the proposal (at pages 2939–2947) the agency thoroughly explained its scientific and regulatory foundations for evaluating drug products as therapeutically equivalent. In addition to bioequivalence requirements, FDA controls batch-to-batch consistency through the new drug approval and antibiotic certification processes, the batch certification procedures, the CGMP regulations, and FDA's monitoring of the marketplace. This monitoring program involves a continuous effort to detect the occasional problems that may be associated with marketed prescription drug products and includes factory inspections, the Quality Assurance Program for Selected Marketed Drugs, the Drug Product Problem Reporting Program, the Antibiotic Post-Certification Sampling Program, the District-Initiated Sampling Program, the Government-Wide Quality Assurance Program, the Maximum Allowable Cost (MAC) Program, the Biopharmaceutics Research Program, manufacturers' reports of problems involving their own drug products, and manufacturers' reports of problems involving competitors' drug products. FDA believes that these diverse programs, each with different scope and purpose but somewhat overlapping perspectives on the prescription drug market, provide assurance that manufacturers and drug products deviating from established requirements will be detected with reasonable promptness. In addition, as explained in Part V below, the recent FDA *Analysis of Prescription Drug Recall Rates* showed that the recall rate for the population of drug products most likely to be the subject of drug product substitution was very low. This demonstrates that consumers, physicians, and pharmacists are very unlikely to encounter a multisource therapeutically equivalent drug product that will be the subject of a recall. Finally, as explained in the response to comment 32 above, regulatory action against violative drug products is independent of the inclusion of products in the List. Marketed products will not be removed from the List until completion of FDA proceedings to withdraw approval of the product under section 505 or 507, as applicable. However, FDA will revise its listed therapeutic equivalence evaluation if warranted by a change in the information in FDA files concerning a particular drug product.

36. One comment argued that in promoting drug product substitution, FDA has failed to consider the economic and public health aspects of "look-alike" drugs. The comment said the implications of "look-alikes" for patient safety are a serious concern: FDA recalls totaled nearly 2,000 over a recent 6-year period, and, according to the comment, the recall rate is many times higher for nonresearch-based manufacturers of generics than for research-intensive companies. The comment said that to the extent that lower-cost generic products are substituted for brand-name drugs, it is likely that generic drugs will have an ever-increasing share of the market, and it is reasonable to expect that the necessity for recalls, because of potentially dangerous mistakes, will increase proportionately. Furthermore, the comment said that with increased substitution, confusion by the consumer of manufacturer identity associated with "look-alike's" may be significant. For example, the comment said that consumers may think they have the brand name drug product, may use the brand name in referring to the look-alike, or may even mix the look-alike with the brand name product in the same bottle. Prompt manufacturer identification, the comment said, is essential to effective drug enforcement, and such identification can easily be delayed or even become impossible with look-alike's.

The agency disagrees with this comment. First of all, for the reasons set forth in the responses to comments 10 and 11 in Part II, FDA disagrees that the purpose of the List is to promote drug product substitution. In addition, the comment's reference to 2,000 recalls over a 6-year period mainly includes products which either do not require NDA's, or which require approved NDA's but which have been marketed illegally. Only about 1 percent of the 2,000 recalls involved approved drug products. It is thus invalid to assume that the approved drug product marketplace is filled with deficient drug products. The agency believes it is especially important, because of the many generic drugs available, whether or not they duplicate the appearance of brand name products, to publish a list of approved prescription drug products that meet FDA requirements and which identifies those products that are therapeutically equivalent, in order to help minimize the chance that products that are not therapeutically equivalent or that are unapproved are used in filling prescriptions. The agency recognizes the need for consumers to be informed when drug substitution occurs in order to prevent them from receiving another product without their knowledge. However, the agency has no evidence to warrant changing its position that the substitution of approved therapeutically equivalent "look-alike" products does not pose any significant problem.

37. One comment said the findings and recommendations of the 1974 OTA Report are presented in a selective, unbalanced, and self-serving manner by FDA in the proposal and that in citing quotations from Congressional hearings on the OTA Report, FDA quotes only a few select favorable statements. Furthermore, the comment said that Recommendation 11 of the OTC Report, which called for an official list of "interchangeable" drug products, was contingent on "considerations of current technology and of technology that we believe could be developed within the next few years." The comment stressed that among the deficits listed in the 1974 OTA Report were those associated with "current standards, particularly compendial standards." These standards, said the commenter, are still deficient, dissolution testing standards remain inadequate, there continues to be a compendial lag in adoption of new methodology, and manufacturer inspections are sporadic. The comment said that if FDA claims it has met the OTA's prerequisites to the preparation of a list proposed under Recommendation 11, it should place its case before an appropriate outside group of pharmaceutical and medical scientists for evaluations.

The agency disagrees that any attempt was made to selectively quote, to FDA's benefit, the recommendations of the 1974 OTA Report. Its

recommendations have been a matter of public record since July, 1974. Recommendation 11, referred to by the comment, proposed the establishment of an official list of drug products evaluated for therapeutic equivalence. The completion of other FDA actions, as explained in the proposal, now makes it feasible for FDA to implement this recommendation. Regarding the comment that compendial standards and dissolution testing standards are deficient, the agency's response to comment 27 above refutes that assertion. In addition, the response to comment 28 above addresses the charge regarding a compendial lag.

38. A comment pointed out that FDA makes definitive evaluations about therapeutic equivalency while at the same time makeing several disclaimers of responsibility for any consequences of these evaluations. The following examples were given. (1) FDA makes no recommendation as to which products persons should purchase, prescribe, or dispense or which products whould be avoided. (2) Because therapeutically equivalent drug products may vary as to color, shape, taste, or packaging, patients may not perceive them as identical or equally acceptable, and for this reason FDA should not state that such drug products are substitutable or interchangeable in all cases. (3) It is sound and appropriate for FDA and the public to rely on the requirements of law, compendial standards, and the drug approval process; however, FDA does not require the public to rely on these regulatory controls or to accept this conclusion. (4) FDA's evaluations of therapeutic equivalence are not binding on any State, physician, pharmacist, or patient.

The agency advises that it did not make any of the statements cited by the comment as disclaimers of responsibility for consequences of therapeutic equivalence evaluations. The proposal pointed out in explaining the legal status of the List that it does not constitute an order or a rule, impose a requirement or restriction upon any person, interpret or apply the act in a manner that creates any obligation on any person, or make a recommendation as to which products persons should purchase, prescribe, or dispense, or conversely, which products should be avoided. Further, because FDA obviously is not the prescriber or the dispenser, it is not in a position to determine whether different drug products are substitutable or interchangeable for use by a particular patient; this judgment rests with the practitioner or dispenser, who, in prescribing and dispensing drug products, can take into consideration the unique characteristics, needs, or problems of the patient. This responsibility is explained in the preface to the List under the heading "E. Precautions to Users of the List."

39. One comment suggested that FDA should publish a list of all prescription drug products marketed in the United States under existing regulations and summarize the specific regulatory standards that have been applied to the individual products and the degree to which producers and their products have complied with these standards. The comment said that such a list should include the following drug products: (1) "Grandfathered" drugs, (2) "old" drugs not subjected to DESI review, (3) "old" drugs subjected to, and passed by, DESI, (4) "old" drugs subjected to DESI but put in possibly effective, or ineffective status, (5) new drugs covered by NDA's or Form-5's, (6) new drugs covered by ANDA's or Form-6's, (7) drugs in interstate commerce but not currently in any of the categories, and (8) drugs in intrastate commerce and not subject to FDA authority. The comment also said FDA should make no representations concerning "equivalency" or "interchangeability".

The agency agrees that the availability of such a list would be desirable, but it does not agree that agency recommendations concerning therapeutic equivalence on drug products which are the subject of approved applications for safety and effectiveness should be withheld unless such a comprehensive list is available. Such a list would be extremely difficult to develop and keep current. Through publication of the List, FDA will make known those drug products it has reviewed and approved. The List represents the vast majority of prescription drugs used in this country.

IV. Specific Criteria Used in Preparation of List

40. Several comments objected to the exclusion of pre-1938 drugs from the List. The comments said that their exclusion was illogical and seriously restricted the usefulness of the List, since pre-1938 drugs represent the bulk of those drugs which are available from multiple sources. The comments also said that the pre-1938 drugs should be included in the List because most of these drugs are contained in the USP and thus are required to meet compendial standards of strength, quality, and purity. Therefore, it was stated, any pre-1938 drug for which compendial standards exist should be considered pharmaceutically equivalent and available for substitution unless there is evidence of a bioequivalence problem. One comment recommended that until pre-1938 drugs are included in the List, FDA should include prominent statements on the cover and title page explaining their exclusion.

The agency believes that pre-1938 drugs, including those in the USP, should be excluded from the List because these drugs are not the subject of approved NDA's. The List only contains information on products approved through the preclearance procedures of the act. FDA is able to evaluate as therapeutically equivalent only those drug products that the agency has had the authority and opportunity to evaluate and ensure for safety, effectiveness, and quality. The agency agrees, however, that pre-1938 drugs should be incorporated into the List once the information necessary to ensure their safety, effectiveness, and quality is available. The agency notes that the final version of the preface to the List states that pre-1938 drugs not subject to the premarket clearance procedures of the law are excluded from the List.

41. Comments also objected that drugs still being evaluated for effectiveness under the Drug Efficacy Study Implementation (DESI) were excluded from the List. These comments contended that neither the definition of pharmaceutical equivalence nor the definition of bioequivalence includes the concept of effectiveness and that bioavailability is not an issue in determining therapeutic equivalence. Thus, it was argued that the agency's assumption that pharmaceutically equivalent drug products are bioequivalent unless there is evidence to the contrary should also apply to DESI drugs that are pharmaceutically equivalent. The comments contended that this rationale has already been accepted by the Federal Government. because Butazolidin Alka, a drug presently listed as ineffective under DESI, was included in the List of Maximum Allowable Cost (MAC) drugs by the Health Care Financing Administration. The comments said that a drug may not be included on the MAC List if there is any regulatory action to establish a bioequivalence requirement, and the bioavailability issue is not considered in establishing a MAC drug. In publishing the List, the comments said that FDA should follow the same criteria, i.e., one of presumed bioequivalence, and the concept of bioavailability should not be considered.

As stated in the preface to the List, the agency has considered and rejected the option of including drug products still under review in the DESI process. The agency's position is that drug products still being evaluated for effectiveness under DESI should be excluded from the List until such time as the active ingredient or combination of ingredients has been fully evaluated and found to be effective. A primary question that must be answered before a DESI drug product may be fully approved for marketing is whether it is effective for its indications; only after this question has been answered does the secondary question of therapeutic equivalence become relevant.

FDA agrees that therapeutic equivalence theoretically may be possible for less-than-effective drugs. In addition, the agency agrees that bioequivalent and pharmaceutically equivalent drug products may be less than effective. But these factors have not been found to justify the agency's evaluation of the therapeutic equivalence of these drugs for inclusion on the List. At the same time, these factors do not prevent the agency from making a therapeutic equivalence evaluation for a drug for which the Pharmaceutical Reimbursement Board is considering establishing a maximum allowable cost. Phenylbutazone alka was included in the MAC program solely on the basis that at the time there was only a single manufacturer and distributor, even though the drug had been evaluated as less than effective, and administrative steps had been undertaken to remove the drug from the market. The comments were in error in stating that a drug may not be included on the MAC list if there is any regulatory action to establish a bioequivalence requirement. Many drugs for which a bioequivalence requirements is pending are included in the MAC program because FDA has assured the Phamaceutical Reimbursement Board that all current manufacturers of the drug have submitted adequate bioequivalence data to the agency.

42. Several comments said that the List identifies only "actual manufacturers" and unfairly discriminates against products marketed by distributors and relabelers who do not also manufacture the products they market. One comment maintained that the "failure of the List to include distributors keyed to each manufacturer will necessarily result in the users of the List generally perferring to deal with actual manufacturers or manufacturer/distributors since dealing with a distributor would require independent confirmation of the source of its drug product." Finally, a comment suggested that to assist the States in implementing their drug product substitution laws, FDA should require that drug product labels bear the name and address of the approved manufacturer.

The agency believes that the comments have misconstrued the basis on which drug firms are included in the List. The products in the List are identified by the names of the holders of approved applications, which are in most instances the actual manufacturers of the products, rather than by the names of the actual manufacturers themselves. This is because the application holder may have had its product manufactured for it by a contract manufacturer and may simply be distributing the product for which it has obtained approval. (A complete discussion of FDA's determination of "application holder" for purposes of the List can be found in the preface to the List under Part E, "Precautions to Users of the List".)

FDA does not believe that there is a feasible way at this time to maintain an up-to-date and complete list linking the products of each approved application holder with the distributors and relabelers handling those products. Products subject to an approved application are frequently manufactured for distributors, under the distributor's labeling, for marketing by the distributor. Because these distributors often shift their source of supply in the commercial marketplace without informing FDA, even if FDA were to attempt to expand the List to link distributors with holders of approved applications, it would not have ready access to the information necessary to do so.

The agency does not agree that the makeup of the List is such that users will necessarily prefer to deal with holders of approved applications rather than with distributors (i.e., those distributors who do not hold the approved applications for their products). The agency believes that in most cases the labels of products marketed by these distributors also identify (as the manufacturer or packer) the holder of the approved application for the labeled product. This label disclosure permits a would-be purchaser to relate the product to the List in a ready and convenient way. The agency encourages distributors to make the necessary disclosure on the drug product label to assist pharmacists, if they choose to substitute a therapeutically equivalent drug for the one prescribed, to select a drug product supplied by a listed holder of an approved application. Nonetheless, the agency may consider feasible alternatives that would identify distributors who are not the holders of approved applications.

It should be noted that although FDA would encourage labels to disclose voluntarily the name of the holder of the approved application for the product, the agency does not have authority to require such disclosure. The Federal law requires that a drug product label bear the name and place of business of the manufacturer, packer, or distributor (21 U.S.C. 502(b)(1)). The choice of which of these persons or which combination of these persons are to be identified is left to the labeler of the product and to the requirements of State law.

43. One comment stated that FDA should not evaluate as therapeutically equivalent drug products that infringe patents because including such drugs on the List violates constitutional principles as well as patent laws and discourages discovery and disclosure of new inventions. Another comment said that a pharmacist relying on the List may be sued for selling an "unlicensed" generic product. Therefore, the List should mention that FDA does not consider the patent status of drugs.

The patent laws do not have any bearing on the enforcement of the Federal Food, Drug, and Cosmetic Act, and the agency does not consider these laws when reviewing new drug applications and making drug product approval decisions. If a firm submits a new drug application for a patented drug, FDA reviews the application without considering any patent issue. If the application is approvable, it is approved. However, to inform the public of this policy the agency, as requested by the comment, will include a statement in the preface to the List to the effect that the patent status of a drug is not considered by the agency in its review of applications to market drugs.

44. One comment objected to the inclusion of single-source drugs in the List. The comment contended that the presence of single-source items is misleading and could even cause prescribing or dispensing errors. The comment said that physicians or pharmacists might assume, unless they carefully check the List, that different dosage forms or strengths of a drug under a single-source heading are equivalent.

The agency disagrees with the comment and believes that including single-source drug products approved for safety and effectiveness adds to the completeness of the List. The agency is confident that, as a result of their highly

technical and specialized training, practitioners and pharmacists will not assume that different dosage forms or strengths of a drug under a single-source heading are equivalent.

45. One comment noted that the Task Force of the American College of Neuropsychopharmacology's final report, which was recently prepared with the help of FDA staff members, deals with the question of equivalence among different versions of psychotropic drugs and recommends the establishment of criteria for developing bioequivalence data within this product class. According to the comment, the report said that bioinequivalence may occur because of the improper substitution of psychotropic drugs after the repeal of anti-substitution laws. The comment noted that many drugs on the List are psychotropic drugs and are designated as "AA", eligible for substitution. The comment said that the possible hazards to patients who rely on these products could be significant.

The agency agrees with the Task Force of the American College of Neuropsychopharmacology that it would be undesirable to use multisource pyschotropic drug products interchangeably unless their bioequivalence had been established. The Task Force, however, did not address all psychotropic drugs, but specifically addressed the tricyclic antidepressants and phenothiazines. These drugs have been coded to indicate a known or potential bioequivalence problem. The agency has published proposed bioequivalence regulations for these two drug classes requiring both in vivo bioavailability studies and in vitro dissolution testing to establish bioequivalence. (The proposal for tricyclic antidepressants published in the **Federal Register** of February 17, 1978 (43 FR 6965); the proposal for phenothiazines published in the **Federal Register** August 26, 1980 (45 FR 56832).)

46 One comment objected to FDA's position that there may be variations in the labeling instructions for drug administration among pharmaceutically equivalent products and that judgments of therapeutic equivalence can be made only when each product is taken in accordance with its particular labeling directions. The comment argued that because these products are listed as being therapeutically equivalent, they will be considered interchangeable.

The agency disagrees. As stated in the proposal, there may occasionally be variations among pharmaceutically equivalent products in the labeling instructions on dose and administration. For example, a particular brand of an antibiotic might require administration on an empty stomach, while another brand might permit administration without regard to food intake on the basis of blood level studies done after administration in the presence of food. Thus, an FDA evaluation of therapeutic equivalence applies only when these products are taken in accordance with labeling directions for the particular product. The preface to the List, Part E, "Precautions to Users of the List," explains this to practitioners. In addition, the agency's explanation of therapeutically equivalent drug products in this document, in the proposal, and in the preface to the List has included the phrase "when administered to the patient under the conditions specified in the labeling."

47. A few comments objected to FDA's procedure of permitting bioequivalence and therapeutic equivalence to be demonstrated by testing a single lot, especially in the use of controlled-release dosage forms. The comments argued that the results of a test on a single lot are not a sufficient basis for assuming continued equivalence in subsequent manufacturing operations. The comments said that FDA must evaluate a manufacturer's ability to produce bioavailable products on a sustained, on-going basis.

The agency believes that it is neither feasible nor necessary to conduct bioequivalence studies on individual lots of a product. Lot-to-lot uniformity can be assured by in vitro dissolution testing when specifications, manufacturing procedures, and controls are identical for all lots. When deficient dissolution performance or lot-to-lot variability is identified through in vitro dissolution testing, the product will be coded as therapeutically inequivalent even though acceptable bioequivalence has been demonstrated in a single lot. This is the procedure that was followed with imipramine and chlorothiazide tablets.

48. One comment stated that the proposal to restrict maximum allowable drug content variations to 1 percent should be reevaluated. This reevaluation should consider topically, orally, and insertion-administered drug products that are being developed or are on the market that are designed not to release their entire contents from their drug reservoirs during their prescribed dosage interval. The actual potency of these products, the comment said, is not normally the labeled drug content but rather, the labeled rate of drug release for the period of administration. The comment suggested that a more comprehensive format for the List be developed, allowing for the display of release rates and durations as well as total drug contents.

The agency notes that the maximum allowable content variation of 1 percent deals with equivalence among products having the same active ingredient but in somewhat different amounts. The agency uses a criterion of equivalence for products where labeled strengths do not vary by more than 1 percent. Most marketed drug products which vary in labeled amount of active ingredient will vary by more than 1 percent and are therefore considered, by the agency, to be pharmaceutical alternatives, not pharmaceutical equivalents. For example, butabarbital sodium tablets, 15 milligrams (mg) and 16.2 mg, are pharmaceutical alternatives because they vary in labeled amount of active ingredient by more than 1 percent. These two products would not be considered therapeutically equivalent because they are not pharmaceutical equivalents due to the differences in labeled amount of active ingredient. Specialized products in which the drug is released from the dosage form at a controlled rate have been evaluated separately using a criterion of equivalence that considers rate of release from the dosage form.

49. One comment said that FDA should consider how it might communicate potentially meaningful differences in the extent and rate of drug bioavailability over the period of administration for similar controlled-release products. This could be in the form of a quantitative performance or merit index that would provide a method of quantitatively discriminating between individual controlled-release products on the basis of how well these products were able to approach the constant maintenance of a target serum drug level. The comment said that an index would allow FDA to include the quantitative index value for each controlled-release product in future lists. This would provide the prescribing physician or dispensing pharmacist with a means to select the best drug bioavailability profile for each patient and, the comment said, it would ensure that similar controlled-release drug products with differing performance characteristics would not be inadvertently considered therapeutically equivalent.

While this commenter describes interesting criteria for evaluating controlled-release drug products that may deserve further consideration, the agency believes the suggestion is not currently relevant to the List. With regard to controlled-release drug

products, the proposal stated (at p. 2951) that these dosage forms are subject to bioavailability and bioequivalence differences primarily because different firms developing controlled-release products for the same active ingredient rarely employ the same approach to formulating their controlled-release products. The agency believes that different controlled-release dosage forms containing the same active ingredients in equal strengths should not be evaluated as bioequivalent unless equivalence between individual products has been specifically demonstrated through appropriate bioequivalence studies.

50. One comment suggested that an additional code should be added to the List to indicate drug products that are being considered therapeutically inequivalent for reasons of potential differences in a patient's compliance with a prescribed dosage regimen or because of differences in the labeled dosage regimen. The comment stated that all treatment regimens are not likely to be followed equally by self-medicating patients, and some drug products have particular characteristics that can either promote or impede patient compliance with a prescribed treatment regimen.

The agency believes that differences in patient compliance between brands should be minimal because the evaluation of products for therapeutic equivalence has been limited to those involving the same active ingredient, strength, and dosage form. Perhaps the comments were concerned that agency recommendations would extend to comparing controlled-release products or specialized dosage forms with conventional dosage forms. It should be apparent to any reader of the List that this has not occurred. Moreover, except in situations where product equivalence has been demonstrated, comparisons have not been made between controlled-release products. The agency has identified in the proposal actual or potential issues associated with legitimate significant differences between conventional dosage forms of pharmaceutical equivalents. Because each of these situations is unique and needs to be discussed individually, the agency does not agree that a new code would serve any purpose. Although the agency agrees that patient compliance warrants concern, it does not believe that the List is the proper vehicle to attempt to improve patient adherence to treatment regimen.

51. One comment noted that an alphabetical listing of the top 200 drugs for 1977 appeared in the April 1978 issue of *Pharmacy Times*. The comment said that these top 200 drugs represented 68.8 percent of all prescriptions, and that 53 of the top 200 drugs are not listed in FDA's proposed List. The comment said that for the generic copies of these 53 drugs, FDA is unable to make a determination of therapeutic equivalence. The comment also said that these 53 drugs are among the most well known prescription products in America.

The agency notes that the comment named only 16 of the 53 drugs it referred to. These 16 drug products are either pending resolution of safety or effectiveness questions and are listed in the appendix to the List, or are drugs marketed prior to 1938 that are not subject to the premarket clearance procedures of the law. Only those drug products fully reviewed and approved for safety and effectiveness by FDA are included in the List. The Drug Efficacy Study Implementation (DESI) process for 2 of the 16 drug products cited by the comment, Atarax and Aldactone, has recently been completed. These drugs were found to be safe and effective for their intended use and will therefore be included in a future supplement to the List.

52. One comment said that the determinations of therapeutic equivalence are unaccompanied by findings sufficient to apprise affected persons of the bases for such determinations. The comment said that in some cases (e.g., hydralazine), there appears to be no data to support FDA's determinations. The comment said the following information is needed to explain FDA's determinations:

a. For drugs coded "AA": whether such coding is the result of,

(1) Actual in vivo bioequivalence studies,

(2) In vitro bioequivalence studies correlated to in vivo data,

(3) Uncorrelated in vitro data (dissolution, for example),

(4) Data on only some drugs from which the equivalence of others has been presumed,

(5) Data on only one drug product from which the equivalence of others has been presumed, or

(6) The lack of any reports to FDA of equivalence problems.

The comment further said these drugs should be accompanied by information as to which of the "therapeutically equivalent" drugs had undergone the studies required in a full NDA and which drugs had undergone no clinical studies, as well as which drugs had been the subject of actual in vivo bioavailability studies. Other comments said that health professionals should know for which "AA" drugs therapeutic equivalence has been assumed and when it has been demonstrated.

b. For drugs coded "AB": the bioavailability study protocol followed by each manufacturer in demonstrating the bioequivalence of his drug product.

c. For drugs coded "BP": sufficient differentiation between those drug products approved on the basis of clinical studies and those approved without submission and review of such studies. The comment said that merely telling physicians and pharmacists that drug products may not be of equal efficiency without telling them which of those drug products had, in fact, been proven effective in humans may create the misleading impression that all drug products listed as "BP" are of suspect bioavailability or effectiveness. Other comments said that information concerning which "BP" drugs are supported by a full NDA, and is the basis for the determination of safety and effectiveness, should be known to the health professional.

The agency believes that the determinations in the List are accompanied by sufficient explanatory data. A drug product identified with an "AA" code in the List is a pharmaceutically equivalent product with no known or suspected bioequivalence issue. These products have been approved for safety and effectiveness by FDA, manufactured in accordance with current good manufacturing practice regulations, and meet compendial standards. The basis for FDA's evaluation leading to the "AA" code for drug products is discussed in detail in the preface to the List and in the proposal. The agency's approach in deciding which drugs pose bioequivalence problems follows the July 15, 1975 Office of Technology Assessment (OTA) Drug Bioequivalence Panel recommendations, which stated that it is not feasible, necessary, or desirable that studies of bioavailability be conducted for all drugs or drug products. To further subdivide code "AA" to indicate which drug products had gone through clinical studies and which drug products had been the subject of actual in vivo bioavailability studies or in vivo/in vitro correlated studies would be contrary to the OTA Panel approach which FDA adopted. Moreover, there is no basis for including information on what drug products meet a nonexistent requirement. For the record, few firms have carried out bioavailability/bioequivalence studies on "AA" class drugs.

It was not FDA's intent to display the bioequivalence/bioavailability study protocol of each manufacturer in the

List. As was explained in the List's preface, the "AB" code identifies an active ingredient in a dosage form for which the submission of bioavailability data is required for approval and indicates that the firm has performed an acceptable bioequivalence study on its product.

Regarding the comment on "BP" drugs, although the agency does not differentiate between those drug products approved on the basis of clinical studies and those drug products approved through the ANDA process, potential bioequivalence problem drugs are coded "AB" when the firm submits adequate data to show that its product is bioequivalent/bioavailable. An example of this is found in the List. Ciba's Metandren (methyltestosterone) tablets are coded "AB" because the firm has submitted adequate data to show bioavailability; all of the other firms' products are coded "BP" because none of the other firms has submitted such data.

In summary, the agency believes that the List, the preamble to the **Federal Register** proposal, and this preamble to the final rule, provide sufficient explanation and background for FDA's determinations of therapeutic equivalence. As explained further in the response to comment 54 below, the agency does not believe it is necessary or practical to include in the List the complete history and data upon which the agency relied to determine the therapeutic equivalence of a drug product.

53. Several comments said that explanations given in the List for the different coding classifications present potential problems. The comments said that some of these definitions are ambiguous and lead to a variety of possible interpretations. Examples of the problems noted by the comments include the definition for "AB" products. The comments said that the definition is unclear whether or not these drugs are substitutable. Regarding classification "AT" (topicals), the comments said that drug products are considered to be pharmaceutically equivalent if they contain the same active ingredients and are identical in strength, dosage form, and route of administration. It would seem resasonable to assume, said the comments, that the different bases used in many ointments and creams, while not active ingredients, significantly affect the rate, duration, and quantity of medication reaching the skin. Regarding classification "BX", the comments said this is a deceptive identification for drug originators because they would have had to provide a documented NDA with adequate clinical data in support of the therapeutic performance of the product. The comments said that the product of any manufacturer who has an original NDA should therefore be specifically identified as such, since the issue of multiple-source equivalence arose only after products were later introduced without requirement of full clinical studies.

The agency concurs with the suggestion to further define "AB". The paragraph in the preface to the List describing the "AB" code has been clarified to state that one product of a drug ingredient heading, coded "AB", is not therapeutically equivalent to a drug product under the same heading which is coded "BD" or "BP". Only those drugs coded "AB" under the ingredient and dosage form headings are recommended as being therapeutically equivalent.

Regarding the suggestion that different bases in topical ointments or creams could affect the rate, duration, and quantity of medication reaching the skin, FDA will review any data that show that a pharmaceutically equivalent product has produced a different therapeutic effect based upon a different base in an ointment or cream. Until that time, FDA will continue to consider products in the same topical dosage form as therapeutically equivalent in the absence of contrary data if they are pharmaceutically equivalent.

Regarding the comment that it was deceptive to identify the drug innovators with a "BX" code since they had to provide a documented NDA with adequate clinical data in support of the therapeutic performance of the product, the agency agrees and will delete the "BX" code from the innovator's product if that product is specifically known not to present the same basis of concern as do the other brands. On the other hand, the fact that an innovator initially performed clinical studies on a product does not necessarily mean that the innovator's product is not subject to the same concerns that led to the inclusion of the "BX" code on other products.

54. Another comment said that the therapeutic equivalence coding system used in the List presents difficulties in correctly identifying the products that are coded. The comment said it is likely that the explanation of the codes will not be read by the typical pharmacist with a busy schedule. The result will be the general assumption that all drugs listed under a particular heading are therapeutically equivalent. In addition, the comment said that the products listed as having bioequivalence problems may require further clarification. For example, phenytoin sodium oral capsule, Dilantin, has been grouped with three products that are probably not bioequivalent. Therefore, the comment said the possibility exists that the reader may incorrectly assume that any one of these drugs can justifiably be substituted for another.

FDA's primary purpose in preparing the List is to provide to the public the agency's information and advice on the therapeutic equivalence of approved multisource drugs. The agency intends to share more detailed information on the therapeutic equivalency of drugs with the States and other interested persons so that they may use this information in their decisions as to which drugs to include in their formulary and which drugs to purchase or dispense. State drug formulary committees have continually asked for the basis of FDA's therapeutic equivalence decisions. Moreover, it is important to explain the bases for these conclusions so that if States disagree, they can act differently. The agency notes, however, that although additional data and information are available upon request, it believes that the preface to the List, the **Federal Register** proposal, and this final rule, provide sufficient explanation and background for FDA's determinations of therapeutic equivalence. The agency does not believe it is necessary or practical to include in the List the complete history and data on a drug product that allowed FDA scientists to determine its therapeutic equivalence. For example, a recent FDA submission to the Pharmaceutical Reimbursement Board to substantiate the claim of the therapeutic equivalency of hydralazine tableted product was over 75 pages long. It is not feasible to disseminate or use as large a document that would result from the inclusion of these data and information for all drugs on the List.

The agency believes that health professionals should have little difficulty in understanding the codes, and will not make general assumptions that all drugs listed under a particular heading are therapeutically equivalent when the drugs have been clearly identified as therapeutically inequivalent. The coding system that FDA has devised is much less complicated than the pharmacological properties of the drug that are contained in the labeling, such as actions, indications, adverse reactions and so on. It should be noted that there were favorable comments from individuals and organizations who were very pleased with format of the List and had no difficulty in correctly identifying the therapeutic equivalence determinations by the displayed code.

V. The Lilly Study

FDA has said it can detect no differences in marketed drug products based on the type or the size of the manufacturer. However, a study conducted by Pauls and Kloer, "FDA Enforcement Activities Within the Pharmaceutical Industry: Analysis of Relative Incentive" (hereafter called the "Lilly study") argued that there are significant differences between products marketed by research-intensive companies and those marketed by non-research-intensive companies. The study concluded that non-research-intensive companies are at least seven times as likely to have a recall as are research-intensive companies. In the category of court actions, the study said that non-research-intensive companies have at least 43 times more court actions than do research-intensive companies. Many of the comments received on the proposal discussed the Lilly study and FDA's criticisms of it in the preamble to the proposal. Some comments defended the Lilly study's division of the industry into research-intensive and non-research-intensive companies, and explained the criteria by which this distinction was made. The comments also defended and further explained the Lilly study's selection process for the research-intensive firms. Other comments criticized Paul deHaan's analysis of the pharmaceutical industry as cited in the proposal and questioned his selection of companies and conclusions made about the industry. One comment showed that when analyzing the industry according to sales, conclusions similar to the Lilly study are reached. Some comments refuted FDA's claim that the Lilly study included recalls that had nothing to do with drug quality and even recalls that did not involve drug products. Another comment criticized FDA for not discussing FDA-initiated court actions, and showed that the incidence of such court actions support the conclusions of the Lilly study. Finally, one comment defended the Lilly study's finding that FDA's enforcement records do not demonstrate product and manufacturer uniformity regarding safe and high quality prescription drugs.

The agency advises that it has consistently disputed the assertion that the Lilly study is valid. The comments indicated that small differences in the selection of research-intensive firms do not have a significant impact on the results of the study. That may be true for the way the recall data are analyzed in the Lilly study, but when coupled with other objections the agency has raised regarding the way in which recall data were treated in the study, selection of the research-intensive firms is critical. One of the major criticisms the agency has made is that the study did not include a denominator by which to compare research-intensive and non-research-intensive and large and small firms. Further, the study tried to compare entities that are not comparable. That is, by comparing the quality of different drug products which have no possibility of being substituted under generic substitution practices, the Lilly study obscured the significance of any quality differences it purports to find. Rather than simply criticize the manner in which the Lilly study was performed, FDA has taken the same recall data and done a more extensive, and FDA believes more valid, analysis of the data. The *Analysis of Prescription Drug Recall Rates* (which is available from the National Technical Information Service (NTIS), Springfield, VA, order No. PB80–182611, and which has also been placed on file in the FDA Hearing Clerk's office) shows no significant quality differences between any meaningful set of comparisons (e.g., products of small firms vs. large firms, PMA vs. non-PMA products, and so on). In the study, the recall rate for the population of drug products most likely to be substituted was shown to be very low. This low rate demonstrates that consumers, physicians, and pharmacists are very unlikely to encounter a multisource therapeutically equivalent drug product in the list that will be the subject of a recall. In addition, and of equal importance, the differences in recall rates of product groups compared in the study are small and dependent on a few large recalls. These differences do not support the contention that a pharmacist or physician can make product selection decisions based upon the supposed superiority of identifiable product groups. The agency agrees with the Lilly study's premise that recall data are perhaps the best available surrogate measure of drug quality. The agency does not, however, agree that the Lilly study is a valid analysis of the FDA recall data, or that the recall data, when properly analyzed, lead to a conclusion that significant differences in drug quality can be ascribed to segments of the drug industry found among the manufacturers of the drugs that the agency has evaluated as therapeutically equivalent.

Regarding the comments' contention that FDA has not commented on that aspect of the Lilly study which compared the rate of court actions against research-intensive and other firms, the agency advises that although it has not analyzed court actions in detail, it is clear to the agency that court cases are not a valid measure of drug defects. Most court cases do not involve violations which reflect on drug quality specifically (in fact, much of the recent drug litigation has been in the area of new drug provisions of the act), and may result from a number of factors which are not relevant to drug quality, such as the firm's perception of the strength of its case, the relative economics of litigating versus market withdrawal, regulatory philosophy and approach, and other factors which are extraneous to the central quality issue.

With respect to the Lilly analysis of the Drug Product Problem Reporting System reports, the agency believes that such reports are not a basis for a reliable index of drug quality. In any voluntary reporting system there are many factors to take into account before a correlation between drug quality and the data can be made. Such systems, while invaluable as an early warning mechanism for problems, are susceptible to manipulation by efforts of some drug firms to discredit others. Certainly the nature of the complaints are not always drug quality related, and their seriousness varies to a considerable degree.

VI. Economic Considerations

A. Anti-Inflationary and Consumer Savings Potential of Drug Substitution

55. Several comments said that drug prices have played little part in the increased cost of health care. Some of the comments questioned the anti-inflationary potential of measures aimed at increased drug substitution, citing the relatively small share of pharmaceutical products in total national health care expenditures and the lower rate of increase in the Consumer Price Index for drugs relative to the total index and to its All Medical Care component.

The agency advises that the proposal acknowledged these points but also pointed out that "these facts do not mean, however, that cost savings in the prescription drug market would not be helpful to the economy, to the consumer, or to the taxpayer. They merely make clear that no single step will be adequate to restrain health costs." The comments have offered nothing to counter this. They argued, in effect, that retarding the rate of price increase of some categories of consumer products is not worth pursuing if there are other categories where prices are rising faster. This argument is not persuasive, especially when offered against a proposal which simply shares with the

public useful information already in FDA's possession.

56. Some comments said that the Federal Trade Commission (FTC) overstated the potential savings from drug substitution. In the proposal, FDA cited the *FTC Staff Report's* conclusion that "the potential for the realization of consumer savings is substantial." Various comments questioned the accuracy of the report's estimate of an upper limit to potential direct savings for drug substitution in the range of $245 million to $408 million. Some of the comments cited a trade publication report of an apparent reduction of the FTC estimate to only $70 million. Other comments questioned the methods and assumptions used by FTC or the validity of the results to which they led.

FDA is not in a position to defend in detail the FTC's methods or results, nor is there any need to do so. The studies cited by FTC, including its own study, focus on potential savings across all or most multisource drugs. FDA does not view the results as projections or forecasts of savings to be achieved, but does believe that they sufficiently demonstrate that the opportunities for savings are substantial, a conclusion not refuted by the comments. Moreover, the propriety and utility of publishing a List that identifies those drugs established as therapeutic equivalents does not depend on a precise estimate of drug substitution savings to consumers. The List is merely a systematic presentation of information used by FDA in its own work. In this respect it is parallel to FDA's earlier publication of a list of inequivalent drugs. Providing reliable information on therapeutically equivalent drugs can only enhance the ability of drug purchasers to recognize and take advantage of opportunities for direct savings by drug selection. Finally, it should be noted that the trade publication citation of an apparent reduction of the FTC estimate to only $70 million was inaccurate and the error was corrected in a later issue to advise that the estimated saving is consistent with the FTC estimate.

57. One comment pointed out that about 45 percent of the dollar value and 55 percent of the prescriptions for all drugs are multisource, and that 12.4 percent of all prescriptions are written generically, suggesting that "only" 32.6 percent of current prescription dollar volume could be multisource drugs subject to further product selection.

According to FDA's calculation, the latter figure should be 34.9 percent. That figure, applied to about $9 billion manufacturers' annual sales volume, translates to about $3.1 billion of manufacturers' sales, and that should be considered the minimum dollar volume of such drugs, since it is unlikely that all generically written prescriptions currently are filled with generic rather than brand name drugs. Regardless of the precise amounts, the agency's decision to publish the List is not contingent on the share of the current prescription dollar volume that is accounted for by multisource drugs.

58. Some comments cited various surveys and other evidence, including those cited in the FTC Staff Report, to indicate that varying proportions of physicians, pharmacists, and even consumers do not favor or practice product substitution. Some comments contended that the exclusion of drugs having known or suspected problems of inequivalence would diminish the potential for savings from product selection. Specifically, some comments indicated that 193 drugs identified as "problem drugs" with respect to bioequivalence in FDA's 1975 list represented an average of about 12 percent of all prescriptions in their respective therapeutic classes and that the currently proposed FDA List shows a net increase of 42 multisource "problem" drugs.

FDA acknowledges that the various multisource drugs are not equally subject to product selection. However, taking the dollar volumes offered at face value and assuming further, hypothetically, that multisource drugs without established equivalence now account for as much as 15 percent of all prescriptions (and hence 35 percent of multisource prescriptions subject to further product selection), the dollar volume of $3.1 billion calculated above would be reduced to $2.0 billion. That amount, which ignores future growth, still represents a considerable target for product selection.

59. Other comments addressed the question of generic vs. brand-name price differentials used in making estimates of direct savings from product selection. It was argued that wholesale price comparisons (based, for example, on *Red Book* figures) are inaccurate and that retail prices should be used. One comment stated, however, that an analysis based on retail prices is almost impossible. Another suggested comparing the average cost of brand drug prescriptions with the average cost for the same drug "when the pharmacist is already engaging in product selection."

FDA agrees that a retail price comparison would be useful (as would a comparison of actual transaction prices at wholesale), provided it distinguished between retail prices charged for generic drugs used to dispense generic prescriptions and brand drugs so used. Unfortunately, the comment did not provide any of the data it recommended. Another comment, however, suggested that consumer savings of at least 20 percent to 40 percent are possible at retail. If it is assumed that average retail savings of no more than 20 to 40 percent might apply to all of the $2 billion sales of multisource drugs subject to further product selection, total additional annual savings of $400 to $800 million are implied. Granted that the current rate of product substitution is well below 100 percent and is unlikely to reach 100 percent, the savings increment will be smaller in proportion to the actual rate of substitution ultimately expected. A rate of 50 percent, for example, would imply additional consumer savings of $200 to $400 million a year without taking account of the rapid prospective growth of multisource drug sales.

B. Federal, Private and State Administrative Costs

60. Several comments contended that the cost to FDA in publishing and maintaining the List could amount to hundreds of thousands of dollars and that manufacturers would have to incur costs of monitoring the List to assure its accuracy.

The agency advises that generating and keeping track of the information that will appear in the List is an internal cost that FDA will incur whether it publishes the List or not. There will be a modest internal cost increment for compilation and computer services to prepare annual issues and monthly updates of the List, but the only significant Federal costs of keeping the List current and publicly available will be those for printing, subscription list maintenance, and mailing by the Superintendent of Documents. FDA expects interest in the list to be sufficiently extensive to ensure subscription revenues adequate to cover these costs, based on an annual subscription rate of $20 ($25 if mailed to a foreign address). Assuming an external subscription volume of 10,000 and internal use of as much as 2,000, revenues from the mail subscription service would be approximately $200,000. The total printing costs for internal distribution would be less than $10,000.

Many State governments will reference the FDA List as the official formularly. They will either print and sell their own copies or recommend a subscription to the FDA List. The annual subscription cost of $20 per copy should cover State-generated demands also. The total demand for the List, direct and

indirect, is uncertain. In addition to retail and hospital pharmacies, physicians and libraries may also want to have access to the List. Clearly, however, the subscription method ensures that total printing and distribution costs will not exceed public wilingness to pay.

Finally, FDA sees no reason to believe that drug industry costs to review the updates of the List for omissions and accuracy would be other than insignificant, and no specific figure was offered by the comments.

61. Another comment said that administrative expenses to State governments in promoting generic substitution may cancel out any consumer savings and, further, that the FDA List will not lessen the expenses of these State activities.

The agency advises that the 46 States that have enacted drug product selection laws (almost half of which have been adopted since 1977) did so for their own reasons, and not to create a market for the FDA List. Conversely, the value of the List does not depend solely on its utility in State efforts to promote product selection. If the availability of a convenient and reliable List of therapeutically equivalent drugs leads to an increase of no more than 1 or 2 percent of prescriptions written and dispensed generically, multi-million dollar savings in drug costs would be realized each year. Similarly, as indicated in the proposal, the FDA List can help States in their own drug purchase programs, and eight States have requested such assistance. It should be noted that FDA's proposal also responds to the requests of at least 19 States for assistance in preparing formularies in support of their product selection laws. Providing a master List that could be used or adapted by each State for its own circumstances is clearly more cost-effective for FDA than assisting each State individually. The comments seemed to suggest, however, that FDA should not provide such a List unless the State programs are demonstrably cost-effective and/or the List will demonstrably reduce State administrative costs for the programs. The agency disagrees. Regarding the comment that the List will not ease State costs of developing formularies, the only evidence offered is that no formulary, including FDA's List, has been or can be used without review and adaptation to the needs of each State. The agency believes it is precisely the existence of a master List to be reviewed and adapted that offers economies to the States in the "start-up" costs of developing formularies and to FDA in assisting them.

C. Indirect Economic Effects

62. Several comments said that expenditures for drugs are the most cost effective in the health care ystem. The comments pointed out that drug therapy at modest cost may reduce the need for hospitalization at very high cost, and cited examples of new drug developments having that effect. Therefore, it was argued, regulating the drug market is a case of misplaced priorities in the control of health care costs.

Regarding the cost-effectiveness of drugs, FDA can only agree and would add that drugs are very cost effective when they reduce death and suffering as well as when they avoid hospitalization costs. The agency does not agree, however, that the social worth of a product is a valid reason for failing to reveal information useful to its purchasers, or that providing such information amounts to misplaced regulation of the market when it is fully expected to improve the efficiency of the market.

63. Several comments said that the promotion of drug substitution will divert revenues from research-intensive companies and thereby discourage research and development of new drug products. The comments pointed out that drug research and development, conducted by many brand name manufacturers, is financed almost exclusively from sales revenues. They argued that a reduction of such revenues would reduce incentives to "invest" in research and development and that this in turn would result in reduced introduction of innovative drugs with consequent long-term health benefit losses to consumers, and in adverse balance of payments effects due to impacts on U.S. drug exports and shifting of U.S. drug company research to foreign countries. Other comments said that through the List, FDA is encouraging a market which favors noninnovating generic product manufacturers.

The agency notes that these comments were not supported by evidence or analysis exploring the manner or degree of any effects on new drug research activity that might follow from increased generic drug product selection. It appears, however, that any reduction of new drug research incentive to a manufacturer as a result of product substitution would take the form of reductions in the present values of the revenue streams and, hence, in the rates of return expected from newly developed drugs. The *FTC Staff Report* referred to in the January 12, 1979 **Federal Register** proposal cited three separate studies on this topic by academic economists. One study estimated that if consumer savings (and manufacturer revenue losses) amounted to 4 to 11 percent of sales a year by 1984, then 0.6 to 1.7 fewer new single chemical entities might be introduced each year out of an average of 15. Another study estimated that, taking patent periods, profit rates, and revenue patterns into account, increased drug substitution would eliminate less than 4 percent of the present value of the expected stream of profits from an average new chemical entity. The study concluded that this would have negligible effects on drug research incentives and on the rate of innovation. The third study, using a similar model and somewhat different assumptions, estimated that product selection would produce a 10-percent reduction in the expected rate of return on an average new chemical entity and a consequent reduction in industry research and development expenditures of $46 million. The latter figure, however, was obtained by applying the research and development to sales ratios of 11.5 percent to an assumed $400 million reduction of multisource drug sales revenues. This procedure is not implausible, but its result can be regarded only as a benchmark rather than a reliable projection. FDA acknowledges that the effect of increased product substitution on new drug research and development activity cannot be foretold with confidence. No evidence or analysis was offered in the comments, however, to offset the implication of the economic studies cited above that the impact on incentives to research and development expenditures would be no more than moderate and possibly negligible. Further, it seems reasonable to suppose that any reduction in research and development effort would tend to focus on marginal, less financially attractive projects. Since substantial consumer savings appear to be required in order to produce anything more than small changes in the economic incentive for research and development, there is no reason to conclude that the tradeoff, if any, is unsatisfactory in terms of the public interest.

Finally, it is necessary to reiterate that in addition to providing support to State drug product selection programs, the FDA List also offers important information to physicians, pharmacists, and consumers who want to avail themselves of it. Because that information can easily be made available, FDA does not agree with the

proposition that the opportunity for a better-informed market for prescription drugs should be rejected simply because some members of the prescription drug industry contend that a less well-informed market is essential to continued drug innovation. If it turns out that a well-informed market is inconsistent with economic incentives for the development of safe and effective new drugs at a rate considered possible and socially desirable, the remedy should not be sought in the economically inefficient device of withholding or obscuring information. A problem of sufficient dimensions to be presented as a public issue would warrant, instead, an open and responsible public solution such as, for example, legislative action on more effective patent protection periods for new drugs. The existence of such a problem, however, has not been established.

64. Other comments contended that the promotion of drug substitution will reduce economic incentives for developing new uses and dosage forms of multisource drugs. The comment said that increased price competition fostered by the List could actually increase incentives to develop and promote new single-source drugs to the extent that it removes the economic incentive to promote, investigate, improve, or monitor multisource drugs. As a result of such a reallocation of research incentives, it was contended, "many multisource drugs may become orphans in favor of new but not necessarily significantly improved single source drugs."

The agency believes that it is by no means obvious that such a trade-off would be unfavorable. The comment did not explain the rationale for its suggestion that increased introductions of new single-source drugs might not include significant improvements. It seems reasonable to assume that a firm committing resources to new drug development would prefer to pursue promising opportunities for significant improvements if they were available. Viewed in this light, such a shift might appear to some as an attractive prospect, even after taking account of the possibility that consumer savings on multisource drugs might be reduced to some degree by more frequent introduction and use of higher-priced single-source drugs. However, the possibility of disincentives to the further improvement of "mature" drugs also warrants consideration independently of any assumptions about associated new drug development efforts. The comments contended that the cost of establishing an approved new use or even dosage form will not be incurred if their potential competitive advantage is nullified by the presence of substitutable equivalent products in the one case or their imminent presence in the other. Although FDA recognizes that it is entirely plausible that such situations may occur, the agency disagrees that such situations would occur generally in an environment of increased duplicate drug product selection. The agency believes that the latter would require, first, that the bulk of postmarket product investigation and evolutionary development occur after the product has not only become multisource but has acquired therapeutically equivalent competitors, rather than during its single-source phase. No evidence was offered by the comments that this would be the case. Second, for a firm that is a major producer of a multisource drug, new uses or dosage forms that result in increased sales of the drug may justify their development cost even though the revenue gains are shared with other producers. Such possibilities are, of course, open to generic as well as brand name manufacturers. Further, even proponents of drug product selection would be naive to suppose that product differentiation and differential pricing, and hence opportunities for profitable product improvement, will universally or quickly disappear from markets for multisource drugs. Granting the qualitative merit of the point, its practical implications are problematic, especially in terms of the likely incremental impact of the FDA List.

65. Several comments argued that the List will have an anticompetitive impact. One comment asserted that this is because the List discriminates by excluding distributors and relabelers of multisource drugs, as well as manufacturers of pre-1938 drugs and post-1938 drugs not approved. It was argued that listed manufacturers would be preferred by users of the List.

Aside from the possibility that distributors might include the names of manufacturers on their labeling, the agency believes that there is little merit in this contention. It appears relevant mainly to purchasing by pharmacies and it is difficult to give weight to the suggestion that such purchasers would remain ignorant of the identities of source manufacturers or would be significantly deterred by procedures for independent confirmation of the source if that were required. The issue of "unapproved" drugs seems hardly relevant inasmuch as the List by definition deals with "approved" drugs and FDA has not "approved" the categories of drugs in question. If the lack of "approved" status has not so far deterred physicians or pharmacists from selecting a drug, there seems little reason to suppose that nonappearance on a List of "approved" drugs would reverse the situation. With respect to the identification of distributors in the List, see the response to comment 42 above.

66. A few comments said that wider use of lower-cost, therapeutically equivalent drug products will adversely affect the quality of health care. It was argued that therapeutic equivalence of a generic product and the product of a research-intensive firm does not mean the health care associated with the use of these drugs is equivalent because the latter product includes an array of informational services that practitioners need to properly understand and prescribe the drug. Fostering the substitution of lower-cost drug products would result in curtailment of these necessary services.

The agency recognizes that valuable informational and educational services are woven into the complex fabric of drug promotional activities. Presumably, however, the period of greatest effort and expenditure for these services—and the period of their greatest need and worth to practitioners— is from the introduction of a new product to its "mature" phase, after which the effort tapers off. Indeed, it appears that the marketing "momentum" of a successfully branded drug that is established during the period of heavy promotional and informational activity may typically carry over far into the period when the drug has accumulated substantial multisource competition. By the time therapeutically equivalent generic products enter the picture, it would seem that most of the advantages to brand marketers and practitioners alike that are cited or alluded to in the comment will have been captured. While it can be agreed, therefore, that useful informational services add to the costs of research-intensive manufacturers, it does not follow that these costs will be inadequately compensated or that physicians will be inadequately informed as a result of such increased generic competition as may be fostered by the List.

D. Absence of a Regulatory Analysis

67. Several comments stated that FDA had proposed a significant regulation requiring regulatory analysis under Executive Order 12044. It was contended that major direct and indirect economic impacts would result from promotion of increased drug substitution, including (a) administrative costs to FDA and to manufacturers, and (b) adverse effects

on research and development of new drug products to the detriment of innovative manufacturers and ultimately to patients. It was asserted that the List will have an overall effect on the economy of more than $100 million and threatens to cost a large segment of the prescription drug industry millions of dollars yearly in diversion of sales revenues to noninnovating firms.

Direct administrative costs of the List to FDA and to manufacturers were discussed earlier and, as stated, FDA has discovered no reason to regard such cost increments as other than very modest. As explained in the proposal (at p. 2953), the agency has determined that the publication of the List is not covered by Executive Order 12044. First, the List is not a regulation, it is a compilation of information available to the agency. Second, the List will not, as the comment contends, have an overall impact on the economy of $100 million through claimed adverse effects on new drug research and development. Regarding this latter contention, it is necessary to distinguish between policies and programs favoring drug product selection and the separate existence of the FDA List. The law and policy of most of the States, in addition to purchasing and welfare programs of the Federal government, now actively promote drug product selection. There is no reason to believe that this objective will not be actively pursued—whether or not the FDA List is made public—since the effort was initiated long before development of the List began. Therefore, any adverse effects on sales revenues and research activities that research-intensive drug firms experience would occur whether or not FDA publishes the List. In determining whether a regulatory analysis is required, therefore, only the incremental impact of the List is relevant.

A $100 million impact on drug research and development expenditures would represent nearly 10 percent of the industry's total domestic research and development effort. To produce such a reduction on the basis of an 11.5 percent R&D to sales ratio would require that the independent impact of the List on industry sales revenues amount to about $870 million. If such a revenue impact were achieved by average savings of 20 to 40 percent on drugs shown on the List as therapeutically equivalent, the sales volume of such drugs subject to these (new) savings would have to be $2.18 to $4.35 billion, that is, new savings of 20 to 40 percent would have to be realized on every dollar of a sales volume equal to about 24 to 48 percent of total prescription drug sales. All of this sales volume, moreover, would have to be found among the drugs identified as therapeutically equivalent in the FDA List and, within those, among drugs subject to low-price and generic competition and on which such savings are not already being realized. Therefore, there is no combination of remotely reasonable assumptions by which the incremental impact of the List on drug substitution could produce a significant effect on drug industry research and development expenditures.

There are major defects also in the additional assertion that diversion of sales revenues from research-intensive to non-innovating drug firms would have a major economic impact requiring a regulatory analysis. It is not evident that revenue losses other than those corresponding to direct consumer savings (which savings were not claimed as a major economic impact subject to regulatory analysis) will necessarily be incurred by research-intensive firms. The latter do, after all, have the option of defending market shares by meeting generic price competition. If they choose to hold to a declining sales volume at higher prices, that presumably is the strategy they regard as more profitable. But there is nothing about the existence of the List that compels research-intensive firms to acquiesce in the diversion of sales revenue to noninnovative firms. In addition, it is not evident that all revenue losses to other drug firms would be to noninnovative firms. Research intensive drug firms also manufacture and distribute a substantial number of generic drugs.

The research-intensive firms who are members of the Pharmaceutical Manufacturers Association account for about 90 percent of total prescription sales. It may be supposed that a one-percentage-point "diversion" of revenue to non-PMA firms would be a less than major economic impact of the proposed List. This might amount to $90 million. In order to suffer such a loss of sales revenue to non-PMA firms, the PMA firms would have to refuse totally to meet price competition on therapeutically equivalent drugs marketed by non-PMA firms. Even assuming such a total refusal to compete, it must be assumed that not all of PMA firms' sales would be lost, since that would imply a total absence of brand loyalty among physicians and a total ability and desire to substitute non-PMA generic drugs at the pharmacy level. Hence, all of a sales volume of drugs considerably greater than $90 million would have to be both subject to and unresponsive to price competition and maximum practicable substitution by therapeutically equivalent non-PMA drugs in order to produce the $90 million transfer. More realistically, the assumption that PMA firms would meet the price competition further increases the dollar value of drugs that would have to meet these conditions. Finally, it would be necessary that all practicable substitutions would have to be achieved on this substantial volume of PMA drug sales—possibly several hundred million dollars—and would also have to be attributable to the availability of the FDA List.

FDA therefore affirms its earlier conclusion that the availability of the List will not produce a major economic impact through retarded drug research and develeopment or through diversion of sales revenues from research-intensive to noninnovative firms.

VII. Procedures for Preparing and Distributing the List

68. Several comments claimed that the List is a cumbersome document containing hundreds of entries and requiring familiarity with various caveats and disclaimers. The comments said its great length, the use of letter codes, the inclusion of single-source drugs, and the prefatory qualifications, as well as the failure to show supporting data, all combine to produce a document that is likely to generate confusion and error. Another comment said the many explanations, codes, and apparent disclaimers contained in the preface are difficult to relate to the information in the List. The List thus falls short as a ready reference source which can be used under daily working conditions. One comment said that because the List is "controversial", it will be necesary to develop special guides, codes, caveats, and disclaimers that provide sufficient information for its proper use. The comment said that this will make the List even more difficult to use and could cause confusion and error.

The agency disagrees that the List will prove as cumbersome and confusing as the comment contends. Drug information as presented by the List is a dynamic and complex area which unavoidably could cause some confusion. As explained in the proposal, FDA, in preparing the List, initially drew from information in its computerized files of approved NDA's, and antibiotic Form 5's. In order to minimize the potential for error, a complete list of approved NDA's, ANDA's, and antibiotic Form 5's, as of April 1978, was published as an interim document in May 1978 and sent to appropriate State officials and agencies, including health officers, boards of pharmacy, and drug

procurement agents, for review and comment. By notice published in the Federal Register of June 30, 1978 (43 FR 28557), this interim list was also made publicly available, with a request for additions, deletions, or corrections. In addition, on two separate occasions, FDA sent to each application holder data worksheets listing its products that FDA had identified as being approved and solicited corrections. The agency received an excellent response with considerable updating information, indicating a serious and careful review by the firms. The agency revised the List in response to these requests. Information regarding approved antibiotic Form 6's (the antibiotic drug submissions analogous to the ANDA) was also included for those antibiotic products last certified within the period of their expiration date. Although the therapeutic equivalence evaluations were not previously circulated, the preface to the List contains extensive explanatory information about them. These evaluations reflect FDA's application of specific criteria to the multisource drug products on the List. The agency believes that the code letters used to explain the basis for these evaluations will not cause confusion once the user becomes familiar with them.

69. Several comments claimed that the List will be virtually obsolete on the day it is published. The comment said that the New York list was subjected to repeated correction, including a notice of changes that was printed within 1 week of publication of the original list, monthly corrections, and at least two major quarterly revisions. Because of the size of the FDA List and the changing nature of the prescription drug market, the comments said it is not possible to publish a currently accurate list. The comments said that if the New York list is now obsolete after only 1 year, the FDA counterpart will be outdated in an even shorter time because FDA is able to investigate the market more rapidly and currently than the New York Department of Health. The comments also said various situations could cause rapid obsolescence such as products no longer being marketed, formulation changes, availability of new dosage forms, new sources of supply, major recalls, and important label changes. To demonstrate the difficulty in keeping these lists updated, the comments compared the List with the New York list. The comments pointed out that the FDA List includes nine product categories coded as nonequivalent, although these same nine products appear on the New York list as therapeutically equivalent. In addition, in New York it is illegal to substitute a tricyclic antidepressant. Nevertheless, several appear on the FDA List as equivalent.

The agency acknowledges the difficulty in keeping the List current. As explained in the response to comment 68, considerable effort was involved in preparing the List, including substantial assistance from the application holders. Because of this initial effort, few corrections were required for a final publication. The agency is planning to provide periodic supplements furnishing, among other things, new drug approval information and, if necessary, revised therapeutic equivalence evaluations. The agency's goal is to provide supplements at monthly intervals at least during the first year after the List is published. An updated List will be published on an annual basis, and each subscription will include all periodic supplements in a given year.

The agency recognizes there may be differences between the List and individual State lists. The FDA List is not an order or a rule, but contains only information and the agency's advice to the public and to the States regarding therapeutic equivalence evaluations, and as such should enable the States to carry out their duties to protect and promote the public health. Thus, a State may or may not adopt the same therapeutic equivalence evaluations as described in this List. Regarding the comment that nine drugs listed in the original New York Equivalency list as therapeutically equivalent are not equivalent in the FDA List, the agency advises that of those nine drug evaluations, three have been revised in the New York list to correspond to the FDA List, two drugs did not have discrepancies in their evaluations but were apparently misread by the commenter, two drugs in the FDA List had errors in coding, and two drugs are listed as having particular problems which are in the process of resolution.

70. One comment said that the preface to the List does not emphasize the key role of pharmacists in exercising independent professional judgments on behalf of patients in drug product selection. Rather than read through the 19 pages of technical language in the preface, the comment said, consumers will simply refer to the List and assume that all drug products that are pharmaceutical equivalents are identical and may be freely interchanged. Another comment said the List should be made available to the professional pharmacist who can then determine whether or not to make the List available to the public.

The agency advises that the purpose of the List is to provide the public with a compilation of drug products that the agency has evaluated and approved for safety and effectiveness. In addition, the List includes therapeutic equivalence evaluations of these approved drug products. The List does not define the role of the pharmacist and the patient in drug product selection. The responsibilities of the pharmacist in the area of drug product substitution are covered by most State drug product selection laws. FDA believes that most consumers will rely on the professional judgments of their physicians and pharmacists in choosing their drug therapy.

71. One comment said that to ensure that pharmacists do in fact substitute lower-priced generic drugs, the public should be adequately advised of FDA's policy. The comment noted that one California survey found that 85 percent of the pharmacists will substitute upon the request of the consumer. However, it was also found that on the average pharmacists were marking up the prices of generics more then they were marking up the prices of brand name drugs. In other words, pharmacists were not passing the cost savings in full to consumers. Instead, they were making higher profits on generics. Therefore, in the public interest, the comment recommended that FDA distribute the List and initiate a program to fully inform consumers of their right to request lower-priced therapeutically equivalent drug products. One means of doing this, the comment suggested, would be an educational program by FDA to promote consumer knowledge of generics and their availability and lower cost.

The agency advises that the List is publicly available, and its availability has received widespread attention in the media. The Department of Health and Human Services generally engages in a number of well-publicized programs to notify consumers that lower-priced drugs may be available. For example, the Maximum Allowable Cost (MAC) program's "Guide to Prescription Drug Costs," is a well-known reference for pharmacists and physicians. FDA believes that through these mechanisms, plus others that will accompany publication of this List, including its use by State governments, the public will be well aware of the availability of less expensive therapeutically equivalent drugs.

72. One comment said the List should be evaluated on a quarterly basis in a manner that would permit any

interested person to challenge the drugs listed as bioequivalent. The comment said that these challenges should be evaluated by an impartial advisory group outside of FDA consisting of professionals with expertise in such fields as medicine, clinical pharmacology, and associated scientific disciplines. The advisory group should have the authority to recommend the removal of a drug from the List if it decides that there is reasonable doubt that the product in question is actually bioequivalent. The comment said that FDA should remove such products from the List and reinstate only when scientific studies conclusively demonstrate that there is no significant bioequivalence problem.

It is the agency's opinion that such an advisory group is unnecessary because the results hoped to be accomplished by the advisory group can be achieved within the present FDA regulatory framework. Any interested person may at any time submit information to the agency which would challenge any findings in the List, including the determinations of therapeutic equivalence. In addition, FDA ensures the quality of marketed drug products through its many progams to monitor the marketplace. These programs are explained on pages 2946–2947 of the proposal.

The agency will, on a continuing basis, review all new information on drug products included in the List. If the information indicates that the therapeutic equivalency evaluation of a drug product on the List is no longer accurate, the evaluation will be revised accordingly. However, as stated in the response to comment 32 of this preamble, the sole criterion for inclusion of a marketed product in the List is its being the subject of an approved application. Marketed products will not be removed from the List until completion of FDA proceedings to withdraw approval of the application under section 505 or 507 of the act, as applicable.

73. One comment noted that the proposal calls for the List to be revised on a quarterly basis and that a method will be devised for publishing all revisions that took place during the preceding 90 days. The comment said that a more practical approach would be to have the revisions made on a continuing basis and published, as made, in the **Federal Register**. Also, additions to the List would be available for substitution on a timely basis. The comment noted that the **Federal Register** is readily available, authoritative, and widely read, and thus the best source for disseminating this information to the largest number of interested parties.

The agency believes that the suggestion to provide List revisions on a continuing basis in the **Federal Register** may have merit. However, for the present time, FDA has decided to publish supplements at monthly intervals (athough the agency originally proposed to revise the List quarterly). The supplements will contain a cumulative index to assist the user in updating the List. The List will be republished annually to include all updated information.

74. Another comment said that FDA should examine the feasibility of having the List printed on microfiche, since microfiche could be used for the entire formulary, and it is easy to use and has an inherent cost savings.

The agency advises that the List is intended, among other things, as a reference source of therapeutic equivalence evaluations to State health officials. The agency believes that many States will generate secondary informational materials for use by their licensed pharmacists and perhaps other health professionals. The use of microform techniques as a format will be considered if there is a demand for the agency List in such a format.

75. One comment said that although offering the List for sale through the Government Printing Office would be adequate for some interested groups, such groups as pharmacies, hospitals, State procurement agencies, and public health clinics should receive a copy of the List directly. If direct mailing is not economically feasible, the comments said that these groups should receive individualized notice of the availability of the List.

The agency advises that the availability of the List is announced in this **Federal Register** document, and copies will be provided to State health agencies. Such actions normally result in a much broader awareness of the availability of the publication through the public and trade press. In addition, the availability of the List will be announced in the *FDA Drug Bulletin*, which is sent approximately every two to three months to health professionals across the country.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201 et seq., 52 Stat. 1040 et seq. as amended (21 U.S.C. 321 et seq.)), the Public Health Service Act (sec. 1 et seq., 58 Stat. 682 et seq. as amended (42 U.S.C. 201 et seq.)), and the Freedom of Information Act (Pub. L. 90–23, 81 Stat. 54–56 as amended by 88 Stat. 1561–1565 (5 U.S.C. 552)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Part 20 is amended in § 20.117 by adding new paragraph (a)(3), to read as follows:

§ 20.117 New drug information.

(a) * * * (3) A listing of new drug applications, abbreviated new drug applications, antibiotic Form 5's, or antibiotic Form 6's, which were approved since 1938 and which are still approved, covering marketed prescription drug products except prescription drug products covered by applications deemed approved under the Drug Amendments of 1962 and not yet determined to be effective in the Drug Efficacy Study Implementation program. The listing includes the name of the active ingredient, the type of dosage form, the route of administration, the trade name of the product, the name of the application holder, and the strength or potency of the product. The listing also includes, for each active ingredient in a particular dosage form for which there is more than one approved application, an evaluation of the therapeutic equivalence of the drug products covered by such applications.

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Effective date. This regulation becomes effective December 1, 1980.

(Secs. 201 et seq., 52 Stat. 1040 et seq. as amended (21 U.S.C. 321 et seq.); sec. 1 et seq., 58 Stat. 682 et seq. as amended (42 U.S.C. 201 et seq.); Pub. L. 90–23, 81 Stat. 54–56 as amended by 88 Stat. 1561–1565 (5 U.S.C. 552))

Dated: October 27, 1980.

Jere E. Goyan,

Commissioner of Food and Drugs.

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